BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

EDITORIAL BOARD

JEROME P. WEBSTER, *Chairman* — MAHLON ASHFORD, *Secretary*

DAVID P. BARR — JOHN G. KIDD — ARCHIBALD MALLOCH

WILLIAM DOCK — ROBERT F. LOEB — WALTER W. PALMER

Editor

MAHLON ASHFORD

VOLUME 24

1948

THE NEW YORK ACADEMY OF MEDICINE
NEW YORK 29, N. Y.

Hospital Library
610.5
N56
A2b
v.24

Medical
Gift
Various Sources

SECOND SERIES JANUARY 1948 VOL. 24, NO. 1

BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

CONTENTS

Recent Advances in Treatment of Lymphomas, Leukemias and Allied Disorders 3
Lloyd F. Craver

Relation of the Adrenals to Immunity 26
Abraham White

Clinical and Experimental Studies on Adrenal Cortical Hyperfunction 32
Louis J. Soffer

Colitis 51
Z. T. Bercovitz

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MAHLON ASHFORD, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

OFFICERS AND STAFF OF THE ACADEMY

1948

President

GEORGE BAEHR

Vice-Presidents

ALEXANDER T. MARTIN — WALDO B. FARNUM — ALLEN O. WHIPPLE

Treasurer

SHEPARD KRECH

Recording Secretary

ROBERT E. POUND

Trustees

*GEORGE BAEHR	CONDICT W. CUTLER, JR.	*ROBERT E. POUND
HENRY W. CAVE	*SHEPARD KRECH	PAUL REZNIKOFF
ARTHUR F. CHACE	WILLIAM S. LADD	CHARLES F. TENNEY
BRADLEY L. COLEY	SETH M. MILLIKEN	ORRIN S. WIGHTMAN
	HAROLD R. MIXSELL	

Council

The President — The Vice-Presidents — The Trustees
The Treasurer — The Recording Secretary
The Chairmen of Standing Committees

Director

HOWARD REID CRAIG

Librarian

ARCHIBALD MALLOCH

Executive Secretary
Public Health Relations Committee

E. H. L. CORWIN

Executive Secretary
Committee on Medical Education

MAHLON ASHFORD

Executive Secretary
Committee on Medical Information

IAGO GALDSTON

Legal Counsel

JOHN W. DAVIS, ESQ.

Library Consultants

LAURA E. SMITH — B. W. WEINBERGER

EDITORIAL BOARD

JEROME P. WEBSTER, *Chairman* — MAHLON ASHFORD, *Secretary*

DAVID P. BARR	ARCHIBALD MALLOCH	PHILIP VAN INGEN
ROBERT F. LOEB	WALTER W. PALMER	KARL VOGEL

* Ex-officio

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

JANUARY 1948

RECENT ADVANCES IN TREATMENT OF LYMPHOMAS, LEUKEMIAS AND ALLIED DISORDERS

*The Bulkley Lecture**

LLOYD F. CRAVER

Physician, The Memorial Hospital

No one can feel satisfied about the treatment of cancer today. While notable progress has been made in the attack on cancer by surgery, x-rays and radium, obviously these agents can succeed in curing the disease only when they can completely remove or destroy all of it, and even if successful may leave the patient badly mutilated. Hence the constant efforts to learn the forces controlling normal and abnormal growth, reflected now in this country by the organization of the Committee on Growth of the Division of Medical Sciences of the National Research Council. The Committee on Growth quite properly has panels on widely diversified branches of knowledge pertaining to growth, such as enzymes, protein chemistry, botany and genetics. Naturally one important aspect of the investigations of factors influencing abnormal growth is a study of the possibility that various agents introduced into the body as a whole may selectively affect neoplastic cells

* Given 28 March 1947, Friday Afternoon Lectures, The New York Academy of Medicine.

and kill such abnormal cells without seriously impairing the patient's health by excessively affecting normal cells.

Such was Ehrlich's hope for a *therapia sterilisans magna* for syphilis. While his hope for syphilis was not realized, his discovery of salvarsan and neosalvarsan represented enormous strides forward in the treatment of that disease. Similarly, with cancer, it is unlikely that any single agent will be found that can be a sterilizing agent, but there is reason to hope that significant progress is possible towards finding selective therapeutic materials that will kill the disease without permanently damaging the patient's health. The sulfonamides, penicillin, and streptomycin have had sufficient success in infections to add greatly to our respect for the possibilities of chemotherapy.

In the investigative work on these problems of learning the causes of, and seeking effective constitutional agents against cancer, the group of neoplastic diseases comprising the lymphomas and leukemias has come into great prominence. Both in animals and in humans these processes are available in abundance, and readily provide measurable features, (biopsies, size of lymph nodes, spleen and liver, basal metabolic rate, blood counts, marrow studies) which enable ready determination of therapeutic effects.

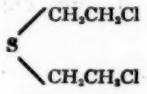
The past decade has witnessed important progress in efforts to control lymphomas and leukemias. These relatively recent advances may be broadly divided into two main categories: 1) chemotherapeutic and 2) radiotherapeutic. In part, the radiotherapeutic category merges with the chemotherapeutic one, in the sense that the selective absorption of the radioactive isotope of phosphorus depends on the metabolic need of cells for phosphorus.

In chemotherapy the agents by means of which recent advances have been made are 1) the nitrogen mustards, 2) urethane and 3) stilbamidine. The older agents, such as arsenic and benzol, have contributed no recent advances, with the possible exception of the report of susceptibility of Furth's chloroleukemia, 1394, of mice to benzene.[1] In the past several years trials of aminopyrine, colchicine and thiouracil[2] in the treatment of leukemia have been disappointing. The workers who treat lymphatic leukemia with extracts of urine or feces from patients having myeloid leukemia, and vice versa, on the intriguing postulation of lymphokentric and myelokentric acid, report partial remissions.[3]

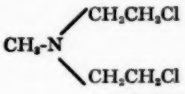
In this paper, therefore, the discussion of chemotherapy will be directed mainly towards the nitrogen mustards, since they currently are in the limelight, and some mention will be made of urethane and stilbamidine, since they too have very recently come to notice.

The Nitrogen Mustards

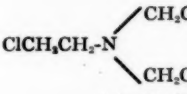
These are nitrogenous analogues of mustard gas, bis(β-chloroethyl) sulfide, as shown by the following structural formulae:



(mustard gas)



methyl-bis (β-chloroethyl) amine (HN_2)



tris (β-chloroethyl) amine (HN_3)

Following World War I a few reports concerning mustard gas described systemic effects on hematopoietic tissues, gastrointestinal tract, and electrolyte and fluid balance, as well as on the growth of experimental tumors, but in general, between the two wars, very little research was done on chemical warfare agents. Early in World War II the possibility that such agents might be employed caused a resumption of research on their biological effects, and as the nitrogenous analogues of mustard gas were believed to be candidate warfare agents they were produced in quantity and studied intensively. It was soon learned that not only were they powerful vesicants on contact with tissue, but that their absorption systemically resulted in toxic action on various tissues, generally proportionate to the degree of cellular proliferation. Thus the most marked pathological changes are seen in the lymphoid tissues of the thymus, lymph nodes, and spleen, in the bone marrow, and in the intestinal mucosa. Lymphoid tissue throughout the body is rapidly affected, showing disintegration of lymphocytes within 5 to 10 hours,[4] resulting in marked shrinkage in volume of lymphatic tissue. All elements of the hematopoietic system are affected. Lymphopenia is followed by neutropenia, and there may be thrombocytopenia and anemia. Large doses may cause almost complete aplasia of the marrow.

Studies of the nature of the effects of nitrogen mustards on cells

reveal no similarity to the effects of any other chemical agent, but many similarities to the effects of x-rays.[5]

These observations led to the suggestion that these agents might be useful in controlling certain neoplastic processes, particularly those of the lymphoid system.

Since the nitrogen mustards were potential chemical warfare agents the matter of arranging for clinical study of their effects was a governmental function. By coöperation between the Army's Chemical Warfare Service (CWS), the National Defense Research Committee (NDRC), the Committee on Medical Research (CMR), of the Office of Scientific Research and Development (OSRD) of the National Research Council (NRC), and with aid from the Jane Coffins Childs Memorial Fund for Medical Research, the clinical investigative program was formulated, and studies were begun under contract between the OSRD and Yale University.

Accordingly in 1942 and 1943 Gilman, L. S. Goodman, Lindskog and Dougherty at the New Haven Hospital treated a series of 7 patients in far advanced stages of cancer by intravenous injections of *tris* (β-chloroethyl) amine hydrochloride.

The first patient selected, in late 1942 for trial of the *tris* compound (HN_3) was one who had advanced radioresistant lymphosarcoma. He was treated by Lindskog at Yale.[6] The dose chosen, 10 consecutive daily doses of 0.1 mgm of *tris* (β-chloroethyl) amine, based on results in experimental lymphosarcoma in mice, was too large, but produced rapid regression and symptomatic improvement. However in one month the patient's tumor masses recurred. Two additional courses of injections were given, but were productive of only slight temporary benefit, and the patient developed a leukopenia of 200 white cells and a thrombocytopenia of 22,000 platelets, and accompanying slight fever, gingivitis, periodontitis and cutaneous purpura. Death appeared to have been hastened by these effects on the marrow.

Thus, while it was obvious that the drug was so toxic to the marrow that it produced dangerous effects in large doses, the striking regression of large radioresistant masses of lymphosarcoma encouraged further clinical trials, particularly in the lymphomas and leukemias.

The result in this case, and the rapid regression in another case of lymphosarcoma were reported in a restricted communication by Gilman, Goodman, Lindskog and Dougherty, dealing with the first clini-

cal trials of nitrogen mustards on a group of six patients in the terminal stages of various neoplastic diseases.[5]

Soon afterward, at the Billings Hospital in Chicago, Jacobson and his group[7] began the study of the effects of methyl-*bis* (β-chloroethyl) amine on various neoplastic diseases of the lymphatics and blood-forming organs. They were the first to use nitrogen mustard on Hodgkin's disease.

Another group working at the University of Utah (L. S. Goodman and Wintrobe) began work on nitrogen mustards in 1943 and recently published[6] a report on their thirty-four cases, together with 16 treated by Dameshek in Boston, ten treated by M. J. Goodman in Portland, and seven treated by L. S. Goodman and Gilman at New Haven.

In October 1944 by authorization of the Chemical Warfare Service and the National Research Council, Memorial Hospital undertook a study of the clinical effects of methyl *bis* (β-chloroethyl) amine. At the request of Dr. C. P. Rhoads a brief survey of the cases of Hodgkin's disease that Jacobson and his group had treated at the Billings Hospital was made by J. C. Abels and the writer, and convinced us that this compound had something to offer in the palliation of Hodgkin's disease in relief of constitutional symptoms, and in resolution of nodal masses and pulmonary infiltrates, although lesions in the bones did not seem to have responded well. We returned to begin this work with the feeling that while the HN_2 compound could produce remissions of Hodgkin's disease, we wanted to find out if it were any better than x-ray treatment, and in particular whether it could prove to be a reliable resource for those cases that had become refractory to x-ray treatment either by reason of marked generalization or because of genuine radioresistance. Therefore our earlier selections were cases that seemed unsuitable for x-ray treatment, and our early results were rather disappointing. However, as further trials were made it appeared that this chemotherapeutic agent offered another tool for the palliation of Hodgkin's disease and other lymphomatous processes and the leukemias, and the fact that there were many related compounds still to be investigated made it obviously worth while to continue the work.

A most helpful impetus was given to our work when through the initiative of C. P. Rhoads we obtained the assistance of Captain David Karnofsky from Edgewood Arsenal, as he was familiar with the secret prior animal and other investigative work that had been the subject

of restricted reports.

The first open announcement of the work that had been done on the evaluation of the nitrogen mustards was made by Gilman and Philips of the Pharmacology Section of the Medical Division of the Chemical Warfare Service in Science in April, 1946.[5]

In June 1946 C. P. Rhoads[8] as Chairman of the Committee on Growth of the National Research Council published in the Journal of the American Medical Association an official statement summarizing the therapeutic status of the nitrogen mustards up to that time and announcing the availability of methyl-*bis* (β-chloroethyl) amine hydrochloride for free distribution to qualified institutions for experimental purposes, through the Committee on Growth in coöperation with the Chemical Warfare Service. Since then the material has had fairly wide trial by a good number of investigators in different parts of the country. By far the experience with nitrogen mustards has been mostly with HN_2 (the methyl-*bis* compound).[9] Since there are, as stated by Gilman, literally hundreds of congeners that remain to be synthesized, screened for possible therapeutic, rather than toxic chemical warfare use, and tested, it is evident that the work has barely begun, and it is distinctly possible that far more useful compounds may come to light.

Now, at Memorial Hospital, we have two programs going on side by side. First is the continued further trial of HN_2 and HN_3 on lymphomas and leukemias. HN_2 has come into practically routine trial especially for Hodgkin's disease when the patient has constitutional symptoms resulting from Hodgkin's disease so generalized or if less generalized so much previously treated by x-rays that one hesitates to employ x-ray therapy again. Second, through the Chemotherapy Planning Board of the Sloan-Kettering Institute, as other nitrogen mustard compounds are selected after a screening process, they are tested first on a carefully chosen pilot case in the research ward, and then tried on six cases each of Hodgkin's disease, lymphosarcoma, myeloid leukemia and lymphatic leukemia, either in the research ward or on the regular medical service.

It is too early to report here the results from the newer nitrogen mustard compounds, and therefore this report will deal with cases of lymphomas and leukemias that have been treated by either HN_2 or HN_3. Most of the patients were treated by HN_2.

Dosage and Method of Administration. Methyl *bis* (β-chloroethyl)

amine hydrochloride, a white crystalline powder, is now available packaged, in 20 cc. rubber capped vials, each containing 10 mgm. of the dry powder. Immediately before the material is to be used, 10 cc. of physiological saline solution is injected into the vial, and the vial is shaken to bring the powder into a solution containing 1 mgm. in each cc. The desired dose for one injection, usually 0.1 mgm. per kg. of body weight, is then withdrawn into the syringe, and the remainder of the solution in the vial is discarded. It is recommended that the intravenous injection be made within 5 minutes following the preparation of the solution, to avoid loss of potency because of rapid hydrolysis.

The groups in Chicago and Salt Lake City have routinely adopted the plan of rapidly injecting the nitrogen mustard solution into the rubber tubing of an infusion set through which is running freely and rapidly a small infusion of glucose or saline solution. Their reason for this procedure is to avoid chemical thrombophlebitis. Great care must be taken to avoid letting any of the nitrogen mustard escape into the subcutaneous tissue, but we have found the syringe method satisfactory. The injection need not be made slowly, and it seems to make little difference at what time of day it is given.

The usual dose is 0.1 mgm. per kg. of body weight once a day for four to six consecutive days. At first in some of the more seriously ill patients the individual dose was reduced to 0.05 mgm. per kg. of body weight, but when later we found that patients usually tolerated 0.2 mgm. per kg. it no longer seemed necessary to cut the usual dose in half.

Toxic effects. Escape of even a small amount of nitrogen mustard solution into the subcutaneous tissue will cause local pain, followed by swelling, induration and redness. The resultant thickening of subcutaneous tissue may persist for many weeks. Not infrequently a small thrombus forms at the site of injection, but usually this effect is due to poor technique in the case of HN_2. With HN_3 we encountered some marked thromboses, but they have not produced any serious consequences.

Nausea occurs in most patients in from 1 to several hours following the injection, and about half will have retching and vomiting. These symptoms may last from a few to several hours, but almost invariably by the next day the patient is ready to accept another injection. Pyridoxine 100 mgm. intravenously or intramuscularly administered prefer-

ably one-half hour following the dose of nitrogen mustard, rather than before (since pyridoxine is one of the substances mentioned by Gilman as subject to alteration by nitrogen mustard), may seem to allay the nausea and vomiting. We have not routinely used sedation. Severe vomiting may of course be hazardous in a patient with a hemorrhagic tendency, as in acute leukemia or acute lymphosarcoma. One patient with acute leukemia died, apparently of intracranial hemorrhage, following vomiting after an initial injection of HN_2, and a young man with aggressive lymphosarcoma and purpura developed a remarkable purpura of his whole face following a bout of vomiting after an injection of nitrogen mustard.

Naturally with nausea and vomiting occurring daily for four to six or seven days the patients usually lose weight and may become more or less dehydrated. In many instances, however, following the course of injections, along with the lysis of fever, and relief from toxic symptoms of the disease, the patients develop an unusually strong appetite and rapidly regain weight.

Toxic effects on the hematopoietic system are regularly seen following adequate nitrogen mustard therapy. The white cell count may begin to drop before the course of injections is completed. Often a lymphopenia develops in a few days, and is followed by a granulocytopenia, so that some time within 3 weeks there occurs a more or less marked leukopenia. With larger doses or repeated courses, the white cell count may go down to 1,000, or 500 cells or even lower. No one seems to have observed ulcers or other manifestation of agranulocytosis, strangely enough, in these cases, nevertheless when the white count falls to 1000 or less we usually give penicillin prophylactically. We regard the depression of the white cell count as a measure of the adequacy of therapy.

Presumably because of the longer life of the red cell, anemia usually does not become as evident a sign of the toxic action of the drug as does the leukopenia, and sometimes onset of red cell regeneration is shown by an increase in reticulocyte count when there has been only a mild drop in the red cell count. Some patients having a severe toxic reaction to nitrogen mustard may show a rapid drop in hemoglobin. While we have not noted clinical evidence of a hemolytic reaction, Jacobson's group found in selected cases a significant increase in total urobilinogen excretion.

The blood platelets may fall very low in some cases and marked thrombocytopenia may be associated with more or less purpura. On the other hand purpura and petechiae may occasionally be seen in patients whose platelet count is not markedly depressed. In at least two instances in which severe generalized purpura occurred, recovery from this state was followed by a marked and prolonged remission of the lymphomatous process.

In patients in whom anemia, leukopenia, thrombocytopenia and purpura may reasonably be regarded as caused by the disease rather than by previous treatment with some form of radiation therapy or with nitrogen mustard, it may be justifiable to proceed cautiously with nitrogen mustard therapy on the chance that improvement may result. The minimum necessary hematological guide to treatment is a total white cell count daily, and a hemoglobin determination every other day during the period of treatment and at frequent intervals for the next three or four weeks.

No fixed rule can be laid down as to how much nitrogen mustard should be given in one course, or how soon another course should be given. The wide vagaries of lymphomatous and leukemic processes prevent predetermination of exact dosage. Usually the standard course of 4 injections of 0.1 mgm. per kg. of body weight, as recommended by the Committee on Growth to those physicians without previous experience with the drug, is within safe limits, but often in our experience, is insufficient to secure a satisfactory degree or duration of remission. In many cases risk of toxic complications must be assumed if one is to obtain a worthwhile remission. The statement, moreover, that "– immediate systemic reactions would appear to be less severe after chemotherapy with the β-chloroethyl amines than after irradiation –"[6] does not accord with the experience at Memorial Hospital, with the possible exception of those cases that as far as x-ray treatment is concerned would need extensive treatment over the abdomen.

Cases treated. From October, 1944 to March 1, 1947, 114 cases have been treated. Of these, ninety-three cases belong in the lymphoma-leukemia category, and include forty-three cases of Hodgkin's disease, twenty-seven of lymphosarcoma, fourteen of lymphatic leukemia, six of myelogenous leukemia and three of mycosis fungoides.

Results. In diseases so variable as the lymphomas and leukemias and in which a new form of therapy is tested on patients in all stages of the

disease, no statistical analysis is valid on such a relatively small number of cases. However, close observation by those familiar with the behavior of these diseases untreated, or treated by irradiation, does permit at this time confirmation of the few published reports that nitrogen mustards undoubtedly have a beneficial effect on these types of neoplastic disease, and justifies the prediction that chemotherapy with these or related compounds will play an increasingly important role in the treatment of lymphomas and leukemias in the coming years.

Hodgkin's disease. Forty-three patients have been treated for Hodgkin's disease. Our early results were disappointing because we deliberately chose at first mostly cases that had reached the point of failure with x-ray treatment. Some were so far advanced, with hard resistant fibrous bulky masses of nodes that it would well have been like a miracle if any agent caused remission. Then when we began to choose cases that would have been more favorable for x-ray treatment results began to appear. Then the question naturally arose whether nitrogen mustard therapy is superior to x-ray therapy, whether remissions would be as nearly complete or as long in duration as with x-ray therapy, and whether the toxic effects were less or more severe.

On the basis of our experience we distinctly do not recommend nitrogen mustard as the treatment of choice for either the early localized case of Hodgkin's disease, or for the case with beginning generalization in which the disease is still rather regionally localized and in which there are as yet no marked constitutional symptoms. Such cases as a rule will be much better cared for by proper x-ray therapy, with much more likelihood of a good result lasting for a good period, and with less toxic reaction to the treatment.

It is with the cases of more or less generalized Hodgkin's disease, having constitutional symptoms, such as fever, sweating, and itching, that the question arises whether they may best be treated by nitrogen mustard or by x-rays. It seems clear that in perhaps the majority of such cases, if the patient is in good condition, has no evidence of extensive marrow infiltration, and has a fairly good hemoglobin and a normal or elevated white cell count, he may obtain a remission within a week or ten days by means of nitrogen mustard injections, whereas to obtain a result with x-ray treatment might require about 3 or 4 weeks of irradiation daily or every other day. If the patient lives at some distance from the hospital it would be preferable in this type of case for

him to be hospitalized for either type of treatment. While most of our nitrogen mustard patients have been hospitalized it has been found practicable to treat some as out-patients, who live near enough so that they can reach home before the nausea and vomiting begin. One gains the impression also, in this type of case that the after effects in terms of hematopoietic depression may be less prolonged after a course of nitrogen mustard than after a therapeutically equivalent course of x-ray therapy. Unfortunately our impression is that the remissions that follow use of nitrogen mustards in this type of case tend to be considerably shorter. This matter of shorter remission is difficult to assay, and certainly in some cases we have seen fully as good a result if not better than might have been expected from x-ray treatment. These results consist usually of partial reduction of nodes, in the deep as well as the superficial chains, partial clearing of pulmonary deposits, some shrinkage of enlarged livers and spleens, and a fairly rapid disappearance of fever, sweating and other signs of toxicity. Itching and bone lesions have not responded particularly well.

The more aggressive the course of the Hodgkin's disease the briefer have been the remissions following nitrogen mustard treatment.

In the far advanced cases, with very bulky granulomatous masses or with anemia, cachexia and hypoproteinemia, nitrogen mustard seldom does more than produce a slight and brief remission.

Lymphosarcoma. Twenty-seven patients have been treated for lymphosarcoma. The aggressive acute lymphosarcomas do not respond well as a whole, either to nitrogen mustard or x-ray therapy. Either agent may produce some temporary palliation and shrinkage of tumor masses or nodules, but such effects mean little in the general rapid progression of the disease. They may be treated with repeated or heavy courses of nitrogen mustard to the point of severe leukopenia, thrombocytopenia, purpura, and anemia, yet the disease shows little response and progresses rapidly to a fatal termination.

In less aggressive generalized types of lymphosarcoma the palliation may be somewhat better, and in some cases, if dosage is pushed far enough, a remission of a few to several months may be obtained, comparable to that seen in Hodgkin's disease.

In a few cases of so-called lympholeukosarcoma (lymphosarcoma with a leukemic blood picture) remissions of several months have been obtained.

In follicular lymphoma results have so far been rather mediocre. It would seem advisable however to have more experience with this type of case. Its usual sensitivity to x-ray therapy would suggest that by and large these cases should respond well to nitrogen mustard, if the biological action of this chemical is similar to that of x-rays. A probable explanation for the mediocre results in some cases as diagnosed by biopsy is the same as the explanation for the failure of some such cases to respond as well as expected to x-ray therapy; that is, that the biopsy is misleading, in that much of the process has gone on to full blown reticulum cell sarcoma.

Lymphatic leukemia. Fourteen patients with lymphatic leukemia have been treated. In some chronic cases the white cell count has fallen and there has been some reduction in the size and consistence of the enlarged liver, spleen and nodes, but usually the differential white cell count, when there have been 90 to 100 per cent lymphocytes, is not changed, and there is seldom evidence of red cell regeneration.

Myelogenous leukemia. Six patients with myelogenous leukemia have been treated. Remissions may result but do not last more than a month or two.

The acute leukemias have in our experience shown an unsatisfactory response to the methyl *bis* or the *tris* compounds. One of the other congeners seems to offer more promise in the leukemias, but further experience and testing of other compounds seems necessary before attempting to assay the value of nitrogen mustard therapy for the leukemias.

Mycosis fungoides. Only 3 patients with mycosis fungoides have been treated. In one patient with bulky generalized skin tumors the response was rapid and there resulted about a 75 per cent regression of the tumors. Relapse however was equally prompt, and a second course, which was almost followed by death of the patient with severe leukopenia, thrombocytopenia and purpura, was likewise followed by a partial regression, but again the relapse was rapid and the disease progressed steadily in a patient growing gradually weaker, and continuing to have anemia, leukopenia and a low platelet count so that neither further nitrogen mustard therapy nor any adequate amount of x-ray therapy could be risked.

To sum up, then, the present status of nitrogen mustard therapy for lymphomas and leukemias, as judged by our own experience and

what has been learned from others, the following may be said:

1. The nitrogen mustard compounds *used so far* have not cured, nor have they shown evidence indicating a possibility that they can cure, any form of lymphoma or leukemia.

2. Methyl-*bis* (β-chloroethyl) amine hydrochloride and *tris* (β-chloroethyl) amine hydrochloride, the two compounds almost exclusively tried up to now, may have marked palliative effects, particularly in Hodgkin's disease, in which especially the detoxifying effects on patients with generalizing disease may be gratifying and more easily accomplished than by x-ray therapy.

3. Remissions, when produced, are disappointingly short, as a rule. Some longer remissions have been produced in some cases by more aggressive dosage, that entailed hematological hazards that were unpleasant and sometimes dangerous.

4. For best effects on early strictly localized lymphomas, on lymphomas beginning to spread but still relatively regionally localized, and on bulky lymphomatous or leukemic masses, in general, local x-ray therapy is superior.

5. There is no basis for general competition between x-ray therapy and nitrogen mustard therapy. The availability of nitrogen mustards affords an additional means of therapy, useful for selected cases or stages of the disease, especially Hodgkin's disease.

6. To this summary should be added:

a) Early results of one and possibly two of the newer nitrogen mustard compounds indicate the possibility of better palliation of leukemia than with the methyl-*bis* or *tris* compounds.

b) The results already seen with these agents that were prepared primarily for chemical warfare rather than therapeutic purposes, and the fact that "literally hundreds of congeners remain to be synthesized and evaluated"[6] offers distinctly the hope that, as has been true of chemotherapy for infections, other compounds far more effective therapeutically may be found.

It was of interest to observe recently in an advanced case of Hodgkin's disease treated by HN_2 an almost complete remission of quadriplegia, a result such as theretofore had been witnessed only following intensive local x-ray therapy to the spinal cord.

Stilbamidine (di-amidine-stilbene di-isethionate) and Pentamidine for Multiple Myeloma: Snapper,[10, 11, 12] in recent communications has

reported the relief of pain in most cases of multiple myeloma by 15 or more intravenous or intramuscular injections of 150 mgm. of stilbamidine or 20 to 30 intramuscular injections of 100 mgm. of pentamidine, provided the patients were kept on a diet low in animal protein.

He found changes in the nucleoprotein of the cytoplasm of the myeloma cells in cases treated with stilbamidine, interpreted as precipitates of ribose nucleic acid, concludes that the metabolism of the myeloma cells is disturbed by stilbamidine, and infers that the abolition of pain is brought about by an arrest of proliferation of the myeloma cells in bone. In some instances partial recalcification and healing of bone lesions was observed.

In four of twenty patients treated with stilbamidine a late sign of intoxication was a dissociated anesthesia in the trigeminal area, beginning two and one-half to five months following the treatment.

Snapper advises great caution in use of the drug in patients with renal failure. He states that the treatment merely checks the disease, but does not cure it.

Urethane for Leukemia: Haddow and his group[13] in testing the effect of carbamates, particularly urethane, on malignant neoplasms, noted that after protracted administration a leukopenia occurred. This observation suggested trial of this chemical in cases of leukemia.

They published a rather optimistic report of reduction in white cell counts, in size of enlarged spleens and relief of symptoms, and indicated greater effect on the less mature cells.

This report led to trials of urethane in this country. In general the effects have been rather unpredictable. In dosage of about 1 gm. three times a day in adults only moderate toxicity results (nausea, vomiting, and some drowsiness); but a good effect on the leukemia is found in only about one-third of the cases, and usually only after administration of the drug has been continued steadily for a month.

Radiation Therapy: In recent years radiation therapy of lymphomas and leukemias has been accomplished either by external irradiation with x-rays, by means of various techniques, or internal irradiation by means of radioactive isotopes.

The radioactive isotopes that have been used, in the lymphoma-leukemia field are chiefly radiosodium, radiophosphorus and radiomanganese. Of these, radiophosphorus has had the widest use, one of the reasons being that it has a sufficiently long half-life to permit its

shipment considerable distances without undue loss of radioactivity by decay, and another reason being that it is somewhat selectively picked up by the more rapidly growing cells of a leukemic or lymphomatous process. Radiosodium has such a short half-life that its use is confined to clinics near the source of supply. Since sodium is so uniformly distributed throughout the body fluids there is no selective pick up of radiosodium, and its effect, considering also its short half-life of about 15 hours, is more like that of a whole body spray of x-rays. Such a type of treatment may of course be useful in leukemia, and the lack of prolonged radioactivity effects may be at times advantageous.

Just as in chemotherapy of lymphomas and leukemias, barely a beginning has been made, so with the radioactive isotopes. When we consider that there are many whose biological properties and therapeutic possibilities remain to be explored, it seems quite possible that the next several years may witness the discovery of much more effective means of treatment with radioactive isotopes. Robley D. Evans' article[14] in the book "Medical Physics" published 3 years ago listed about 400 radioactive isotopes that had been made by the cyclotron, and in "Science" in June, 1946[15] there was published a list of about 100 isotopes, products of the uranium pile.

Radiophosphorus, or P^{32}, formerly made in the cyclotron by the bombardment of phosphorus with deuterons (heavy hydrogen nuclei) is now available from Oak Ridge, and probably eventually will be made available from other uranium piles. P^{32} is so named to indicate that the atom of phosphorus, instead of having a mass of 31 has acquired a mass of 32 by the addition of one neutron to its nucleus, although the nucleus still has the same number (15) of protons or positive charges, and the same number of electrons are still revolving about the nucleus. Hence chemically P^{32} is identical with ordinary phosphorus, P^{31}, and cells will accept P^{32} in their metabolic turn-over of phosphorus as readily as P^{31}.

There are four reasons why radiophosphorus would seem theoretically to offer an approach to an ideal method of treatment of leukemia or lymphoma by irradiation.

1) Selective pick-up of phosphorus by the more rapidly growing cells of leukemia or lymphoma, so that each such cell becomes a source of radiation.

2) Total body distribution of this selective internal irradiation.

3) The half-life of 2 weeks, resulting in the irradiation of succeeding generations of cells over a reasonable period, but not entailing permanent storage of significant amounts of radioactive material as would be the case with a salt of radium, which has a half-life of 1,600 years.

4) The only type of radiation emitted by radiophosphorus is beta radiation having an average energy of 0.6 million electron volts and a maximum energy of 1.8 million electron volts. These beta particles penetrate tissue to an average of only 2 or 3 millimeters and to a maximum of about 7 millimeters.

Unfortunately, while this combination of features suggested the possibility of great efficacy in the treatment of lymphomas and leukemias, and some of the early results in the treatment of leukemia by P^{32} supported such a hope, it soon became evident that P^{32} was not producing cures of leukemia, that it was only moderately helpful in some cases of lymphosarcoma, and that it was not effective in most cases of Hodgkin's disease. Further clinical trials indicated that the shortcoming of P^{32} was simply that it was not sufficiently selective for the types of cells which one wished to affect and that in treating the tumor cells one was unavoidably also affecting normal marrow cells. Persistence in repetition of doses of P^{32} could lead to severe marrow depletion, while still the malignant process remained viable. One may reason that even if one assumed that P^{32} were selectively picked up only by leukemic cells and by no others whatsoever, the very fact that beta rays penetrate up to 6 or 7 millimeters into surrounding cells is sufficient reason to expect that depletion of the marrow would become, as it has been shown to be, the limiting factor in the treatment of leukemia by P^{32}.

Then, when we consider how much intensive local x-ray therapy may be required to cause regression in many cases of lymphosarcoma and Hodgkin's disease, it is easy to see why it is impossible safely to load up the patient's entire body with enough P^{32} to administer an effective therapeutic dose to the enlarged nodes, spleen, and other foci of lymphomatous disease. Much less feasible is it to attempt treatment of such processes as metastatic breast cancer, or osteogenic sarcoma by means of P^{32}. Yet inquiries still come in every week concerning the suitability of such cases as a localized myxosarcoma, or a metastatic melanoma for treatment by radiophosphorus!

Occasionally some very radiosensitive cellular neoplasm such as

metastatic teratoma of the testis has been found to respond temporarily with a good regression following the administration of P^{32}. In leukemia, the acute processes are in general as unsuitable for P^{32} as they would be for whole body roentgen irradiation. The white cell count in such cases may fall rapidly, or local leukemic deposits may regress, but just as with treatment by roentgen rays, the course of the disease as a whole is not favorably affected and may very easily be aggravated.

In June 1945, Shields Warren[16] reported his results in the treatment of 81 cases of leukemia during a period of over 4 years. He had selected cases chiefly of two unfavorable types; those which had become resistant to x-ray therapy after an initial favorable response, and those known to do badly with x-ray therapy, that is, acute leukemias of childhood, and a few moribund patients with chronic leukemia.

Of his sixty-six cases of leukemia, twenty-two had previously been treated, and these included seven cases of acute or subacute leukemia, and fifteen cases of chronic leukemia. In his previously untreated forty-four cases, there were 32 of acute, subacute or monocytic leukemia, and 12 cases of chronic leukemia.

Warren's best results were in the previously untreated chronic and subacute myeloid group, and, curiously, in the previously treated lymphatic group of all types.

An analysis of Warren's 1945 report should dispel any notion that good results were obtained in acute leukemia. From his tables it may be learned that of 9 cases of acute myeloid leukemia none were improved, of 12 cases of acute lymphogenous leukemia only 3 were helped, of 8 cases of unclassifiable acute leukemia none were considered improved, and of 4 cases of monocytic leukemia, none of which had previously been treated, only one was improved.

In February 1946, the Washington University group[17] published an excellent detailed summary of the results of radiophosphorus treatment on a total of 155 cases including 30 cases of polycythemia vera, 94 cases of leukemia, six cases of Hodgkin's disease, nine cases of lymphosarcoma, two cases of mycosis fungoides, and eight cases of multiple myeloma. Thus, of their total of 155 cases, all but six were in the leukemia or lymphoma group, if one includes polycythemia in this group.

The St. Louis group's conclusions as to the value of P^{32} are in essential agreement with those of other writers. For polycythemia vera they

regard P^{32} as the best therapeutic agent available. In chronic myelogenous leukemia they reported that P^{32} produced at least as complete clinical and hematological remissions as x-ray treatment, and a suggestion of about an equal prolongation of life (about 6 months), with the advantage of freedom from radiation sickness. In acute and subacute myelogenous leukemia they observed very little effect on the clinical course. Similarly most cases of acute lymphatic leukemia or leukosarcoma failed to respond favorably. For chronic lymphatic leukemia they regard P^{32} as probably as satisfactory as, but no better than, x-ray treatment. Monocytic leukemia failed to respond to P^{32}. Hodgkin's disease, lymphosarcoma, mycosis fungoides and multiple myeloma did not respond as well to P^{32} as to x-ray treatment.

At Memorial Hospital we recognized early in our work with P^{32} that it alone would not satisfactorily control most of the cases of leukemia, and that it was best regarded as not in competition with x-ray therapy, but as a complementary agent. Therefore, almost from the beginning of our work[18] in 1940, most of the cases received x-ray treatment when it seemed indicated, and P^{32} when there seemed some good reason for its use. We have treated very few cases of Hodgkin's disease with P^{32} because early reports indicated a general agreement on the comparative lack of good results in that disease, and because experience with the amount of x-ray treatment necessary for effective control of Hodgkin's disease indicated the unreasonableness of trying to control it by P^{32}. In a few cases of plasma cell myeloma P^{32} has failed in our hands to have any worthwhile result. In the treatment of lymphosarcoma for the past several years only an occasional case of an unusually radiosensitive type such as some of the follicular lymphosarcomas, is selected for a course of P^{32} as part of the treatment program.

The following tables, compiled by Dr. George H. Parks and Dr. Loton Rasmussen from our records, summarize the comparison of results with P^{32} and with x-rays in a series of cases of leukemia and lymphosarcoma in which both agents were used at different times.

In the treatment of a relatively small number of cases of polycythemia vera our own experience has been mostly with patients living at some distance, so that the hematological effects have not been followed as closely as was desirable. It has seemed that symptomatic improvement was greater than the hematological improvement, and whether results are better in this group than those obtained previously by spray therapy

CHRONIC LEUKEMIA

	Myelogenous	*Lymphatic*	*Total*
Cases Studied	27	27	54
P^{32} and x-rays equally effective in producing remissions	15	9	24
P^{32} more effective than x-rays in producing remissions	1	1	2
P^{32} less effective than x-rays in producing remissions	5	2	7
P^{32} used entirely or almost entirely in producing remissions	4	2	6
P^{32} and x-rays both ineffective	0	2	2
P^{32} produced remissions but too little used for comparison with x-rays	2	11	13
P^{32} more useful because x-rays too toxic to be tolerated	1	0	1
P^{32} less effective than x-rays in treating local manifestations	2	9	11

ACUTE AND SUBACUTE LEUKEMIAS

Total cases studied	31
Cases without remission	25
Cases with remission	6
Remission associated with P^{32} therapy	2
Remission associated with x-ray therapy	2
Remission associated with acute infection and sulfonamide therapy	1
Remission spontaneous	1

LYMPHOSARCOMA

Total cases studied	19
P^{32} and x-rays equally effective	2
P^{32} more effective than x-rays	2
P^{32} less effective than x-rays	10
P^{32} used entirely or almost entirely in producing remissions	2
P^{32} and x-rays both ineffective in producing remissions	3
P^{32} more useful because x-rays too toxic to be tolerated	0
P^{32} less effective than x-rays in treating local manifestations	11

or x-ray treatment of the long bones seems at present doubtful.

Recently attention was called to a belief apparently held by some physicians that treatment by means of radiophosphorus of a patient with polycythemia is likely to induce leukemia. It is fairly common for polycythemia to eventuate in myeloid leukemia or to present a leukemoid picture. In the Mayo Clinic series of 163 cases reported by Tinney, Hall, and Giffin,[19] of 36 patients in whom the disease was of 5 or more years duration, death had occurred in 6 from leukemia or leukemoid reaction. I know of no evidence that has been produced to show that radiation causes or hastens conversion of polycythemia into leukemia, and it seems doubtful that this well-known mode of termination of polycythemia has any particular relation to irradiation. However, it would seem a project well worthy of careful statistical study, to compare cases treated only by phlebotomy, with those treated by phenylhydrazine, those treated by x-rays, by radiophosphorus, and by nitrogen mustards, since conceivably the repeated insults to the marrow by phenylhydrazine, x-rays, radiophosphorus, or nitrogen mustard might tend to evoke a leukemic response.

The following types of cases are the ones that seem most suitable for radiophosphorus therapy.

1. Polycythemia. Since there is a lag in the effect of P^{32}, a patient urgently in need of relief had best have phlebotomy at once.

2. Chronic myeloid leukemia with no marked enlargement of the spleen or liver. Bulky leukemic spleens or livers are probably best treated by local x-ray therapy and in general, the typical previously untreated case with a large spleen will obtain a better all around remission by means of x-ray therapy to the spleen.

3. Chronic lymphatic leukemia presenting rather minimal nodal, splenic and hepatic enlargement. Large nodes, spleens and livers will usually respond better to local x-ray therapy.

4. Cases requiring some maintenance therapy between courses of x-ray treatment may obtain some benefit from P^{32}.

5. Radiosensitive lymphosarcoma may perhaps be partially controlled as far as widespread minimal lesions are concerned, but local deposits of any considerable magnitude will be better controlled by local x-ray therapy.

Conventional Irradiation. Offhand one might think there is nothing to be said about recent advances with respect to conventional x-ray

therapy for leukemias and lymphomas. Certainly it is true that as far as the acute leukemias are concerned conventional irradiation has long been known to be ineffective and often dangerous. In the chronic leukemias, and in Hodgkin's disease and lymphosarcoma, however, considerably improved palliative results are now possible because of:

1. Increased knowledge of, search for, and detection and treatment of obscure lesions, formerly little known, but which are often of more importance to the morbidity of the patient than many of the more obvious lesions. Reference is made here to such lesions as those which may compress the spinal cord, to cortical bone lesions, to gastrointestinal lesions, and to pulmonary parenchymal deposits.

2. Greater precision in application of conventional irradiation to specific lesions with due attention to adequate inclusion of lesions in the beam of irradiation, adequate local dosage, and at the same time avoidance of unnecessary body dose, so as to spare the patient in so far as possible the deleterious effects on his marrow.

3. Recognition of the unicentric origin of many cases of Hodgkin's disease and of some cases of lymphosarcoma, so that early treatment of localized Hodgkin's disease or lymphosarcoma is carried out aggressively, giving the patient a chance, theoretically at least, for cure, certainly for longer palliation, than if just enough treatment is given to produce a regression.

4. Addition of a small dose, 75 to 125 r of total body irradiation in selected cases seems to have prolonged life and delayed relapse in some cases. The difficulty in this connection is in choosing the case in which benefit may be expected. Certainly we can look back and find cases so treated in which there seems to be no question but that they have had much longer remissions than were to be expected, had they received only local therapy.

A recent survey of the 5 year survival figures[20] for lymphomas and leukemias treated at Memorial Hospital from 1930 through 1940 shows in the main an improvement over previously reported results. Hodgkin's disease shows 20.5 per cent 5 year survivals of 283 patients, to be compared with 17.7 per cent of 265 patients treated from 1918 through 1935. Lymphosarcoma shows 26.3 per cent 5 year survivals of 308 patients, to be compared with 15.9 per cent of 132 patients treated from 1918 through 1933. Chronic lymphatic leukemia shows 15.7 per cent 5 year survivals of 125 patients, to be compared with a 5 year

survival of 9 per cent of a group of 77 patients with lymphatic leukemia treated from 1917 to July 1, 1929, from which group was excluded, however, only those cases lost to follow-up within 6 weeks. Chronic myelogenous leukemia shows the poorest survival rate—5.3 per cent 5 year survivals of 57 patients, to be compared with 5.9 per cent previously reported for 68 cases treated from 1917 to July 1, 1929. (Excluded from the latter group were those cases lost to follow-up within 6 weeks.)

These improved survival figures for all but myeloid leukemia reflect almost entirely the results of treatment by roentgen therapy and general supportive measures. They may serve in the future for comparison with results obtained by chemotherapy and isotope therapy.

Some mention should be made of the possibility of radical surgery for certain early and strictly localized cases of Hodgkin's disease and lymphosarcoma. Up to the present surgery in this field has been successful chiefly in certain gastrointestinal lesions, which perhaps have been somewhat atypical. Yet the evidence for unicentric origin of most cases of Hodgkin's disease and some cases of lymphosarcoma seems strong enough to suggest that the possibility of surgical removal should be kept in mind when an early localized lesion of a type that could be removed is found and no evidence of spread can be detected. Such cases are still so rare by the time a diagnosis is made that surgery will probably have to wait a good many years before it can come to play any large part in curative therapy.

To sum up the advance in the treatment of lymphomas and leukemias we may consider (1) what has been accomplished and (2) what seems to be promising.

What has been accomplished: (1) an improvement in palliative results measured both by relief of symptoms and by survival curves in Hodgkin's disease, lymphosarcoma and chronic lymphatic leukemia by roentgen irradiation as a result of greater precision in detection of lesions and in their treatment; (2) additional ways of palliation by means of nitrogen mustards for Hodgkin's disease, and some cases of lymphosarcoma and leukemia, by means of urethane for some cases of leukemia, and by means of stilbamidine for multiple myeloma.

What seems to be promising: (1) the possibility of cure of some cases of Hodgkin's disease and lymphosarcoma if diagnosis can be made early enough to permit obliterative roentgen therapy or perhaps even

radical surgery in cases amenable to such methods; (2) the possibility of development of more specific attack by means of suitable modification of radioactive isotope therapy; (3) the possibility of discovery of much more specifically acting chemotherapeutic agents.

REFERENCES

1. Flory, C. M., Steinhardt, I. D. and Furth, J. Further observations on the effect of benzene on a strain of myeloid chloroleukemia in mice and on changes produced in the leukemic cells by the chemical, *Blood,* 1946, *1*:367.
2. Limarzi, L. H., Kulasavage, R. J. and Pirani, C. L. Effect of thiouracil on leukemia, *Blood,* 1946, *1*:426.
3. Miller, F. R., Herbert, F. A. and Jones, H. W. Treatment of lymphoblastic leukemia with crude myelokentric acid, *Blood,* 1947, *2*:15.
4. Karnofsky, D. A., Craver, L. F., Rhoads, C. R. and Abek, J. C. Evaluation of methyl-bis (beta-chloroethyl) amine hydrochloride and tris (beta-chloroethyl) amine hydrochloride (nitrogen mustards) in the treatment of lymphomas, leukemia and allied diseases. Approaches to tumor chemotherapy, *American Assn. for the Advancement of Science,* 1947, pp. 319-337.
5. Gilman, A. and Philips, R. S. Biological actions and therapeutic applications of the beta-chloroethyl amines and sulfides, *Science,* 1946, *103*:409.
6. Goodman, L. S., Wintrobe, M. M., Demeshek, W., Goodman, M. J., Gilman, A. and McLennan, M. T. Nitrogen mustard therapy; use of methyl-bis (beta-chloroethyl) amine hydrochloride and tris (beta-chloroethyl) amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and allied and miscellaneous disorders, *J.A.M.A.,* 1946, *132*:126.
7. Jacobson, L., Spurr, C. L., Guzman Barron, E. S., Smith, T., Lushbaugh, C. and Dick, G. F. Nitrogen mustard therapy; studies on the effect of methyl-bis (beta-chloroethyl) amine hydrochloride on neoplastic diseases and allied disorders of the hemopoietic system, *J.A.M.A.,* 1946, *132*:263.
8. Rhoads, C. P. Nitrogen mustards in the treatment of neoplastic disease, *J.A.M.A.,* 1946, *131*:856.
9. Alpert, L. E. and Peterson, S. S. Use of nitrogen mustard in the treatment of lymphomata, *Bull. U.S. Army M. Dept.,* 1947, *7*:187.
10. Snapper, I. Influence of stilbamidine on multiple myeloma, *J. Mt. Sinai Hosp.,* 1946, *13*:119.
11. Snapper, I. and Schneid, R. On the influence of stilbamidine upon myeloma cells, *Blood,* 1946, *1*:534.
12. Snapper, I. Stilbamidine and pentamidine in multiple myeloma, *J.A.M.A.,* 1947, *133*:157.
13. Paterson, E., Haddow, A., Ap Thomas, I. and Watkinson, J. M. Leukemia treated with urethane compared with deep x-ray therapy, *Lancet,* 1946, *1*:677.
14. Evans, R. D. Isotopes: radioactive, measurement in *Medical Physics,* Chicago, Year Book Publishers, 1944, p. 643.
15. Announcement from Headquarters, Manhattan Project, Washington, D. C. Availability of radioactive isotopes, *Science,* 1946, *103*:697.
16. Warren, S. Therapeutic use of radioactive phosphorus, *Am. J. M. Sc.,* 1945, *209*:701.
17. Reinhard, E. H., Moore, C. V., Bierbaum, O. S. and Moore, S. Radioactive phosphorus as a therapeutic agent, *J. Lab. & Clin. Med.,* 1946, *31*:107.
18. Craver, L. F. Treatment of leukemia by radioactive phosphorus, *Bull. New York Acad. Med.,* 1942, *18*:254.
19. Tinney, W. S., Hall, B. E. and Giffin, H. Z. Prognosis of polycythemia vera, *Proc. Staff Meet., Mayo Clin.,* 1946, *20*:306.
20. Craver, L. F. Lymphomas and leukemias, *Bull. New York Acad. Med.,* 1947, *23*:79.

RELATION OF THE ADRENALS TO IMMUNITY*

ABRAHAM WHITE

Associate Professor of Physiological Chemistry, Yale University School of Medicine

THE factors which contribute to immunity, both natural and acquired, have been recognized and partially evaluated as a result of experimental and clinical studies of the past sixty years. Among the more important of these factors are the following: 1) genetic, 2) cellular, 3) nutritional, 4) environmental, and 5) hormonal. The present discussion will be concerned chiefly with the relation of hormonal factors to immunity, with particular emphasis on the role of the adrenal cortex, although, as will be indicated, the level of functioning of the adrenal cortex is influenced markedly by at least two of the other factors, namely, nutrition and stimuli present in the environment. The term, immunity, will be used broadly with a connotation of increased resistance to both non-antigenic and antigenic substances, although a consideration of the relation of the adrenal cortex to immunity will be illustrated in part by antibody responses to specific antigens.

Evidence is available from both morphological and physiological studies that the adrenals play a significant role in the defensive mechanisms of the body, particularly against intoxications, infectious diseases and environmental stresses of the type of anoxia and abnormal temperatures. The active participation of the adrenal cortex in these circumstances has long been suspected by pathologists. Hyperemia, edema, hemorrhage, and focal necrosis occur in the adrenal glands in cases of burns of the skin, food or chemical poisoning, and acute infections. Conversely, adrenalectomized animals and patients with Addison's disease succumb readily to drugs, toxins, and stresses in amounts and degree generally innocuous to the normal individual.

Elucidation of the role of the *adrenal cortex* in immunity has been

* From the Department of Physiological Chemistry, Yale University, New Haven, Connecticut. A part of the data included in this paper were obtained from investigations aided by grants from the Josiah Macy, Jr. Foundation and the Fluid Research Fund of the Yale University School of Medicine.
Delivered 8 October, 1947 at the Twentieth Graduate Fortnight of The New York Academy of Medicine.

partially obscured by the numerous immunological studies with the hormone of the *adrenal medulla,* epinephrine, since it is now established clearly that epinephrine is a powerful augmentor of the rate of secretion of the hormones of the adrenal cortex.[1] The normal regulator of adrenal cortical secretion is the trophic hormone of the anterior pituitary gland, adrenotrophin. This pituitary hormone is secreted in greater than normal quantity following exposure of the organism to a wide variety of unrelated stimuli: inanition, alterations in environmental factors such as heat, cold and anoxia, trauma in the form of tissue injury, fractures and hemorrhage, injections of bacterial toxins, certain toxic chemicals (arsenic or benzene), anesthetics (nembutal), foreign proteins, and a variety of substances normally produced in the organism, e.g., histamine, insulin, epinephrine, thyroxine and estrogens.[2] The accelerated release of adrenal cortical hormones, as a result of any of these stimuli, does not occur in the absence of the pituitary, and each stress, therefore, has a common physiological influence, i.e., to increase the output of pituitary adrenotrophic hormone. Thus, augmented secretion of epinephrine in the normal individual will elevate the rate of release of the pituitary adrenotrophic hormone and result in an increased rate of secretion of the hormones of the adrenal cortex. There is, therefore, an intimate physiological relationship between the secretions of the two endocrine glands which constitute the adrenal, namely, the adrenal medulla and the adrenal cortex. As will be indicated, the available evidence suggests strongly that data establishing an increased immunity following epinephrine injection were probably a manifestation of the increased concentration of circulating adrenal cortical steroid hormones resulting from the ability of epinephrine to augment pituitary adrenotrophin secretion.

From the foregoing, it would appear that those physiological processes contributing to immunity and influenced or regulated specifically by adrenal cortical secretion will also be affected by any one of the variety of stimuli which augment pituitary-adrenal cortical secretion. This concept will aid in explaining the similarity of certain phenomena of immunity under widely diverse circumstances.

What do pituitary-adrenal cortical stimulation and the resulting increase in concentration of circulating adrenal cortical steroid hormones, contribute to immunity? This question can be answered in part in terms of the established physiological functions of these steroid hor-

mones, which affect several large categories of metabolic phenomena: 1) water and salt metabolism; 2) protein metabolism; and 3) carbohydrate metabolism. In addition, it has been demonstrated recently that adrenal cortical steroids contribute to certain aspects of immune cellular responses, namely, development of phagocytic cells and production of immune globulin. Whether these known physiological effects of pituitary-adrenal cortical secretion can explain completely the role of this endocrine mechanism in immunity is a problem under investigation in many laboratories.

Data obtained in collaboration with Dr. T. F. Dougherty[3] show that the adrenal cortical steroids have a marked effect on cells long known to be concerned with certain processes of immunity, namely, reticuloendothelial cells. Increased numbers of phagocytic cells develop in lymphoid structures as a result of increased adrenal cortical steroid secretion or injection. The histological picture seen in these circumstances is similar in many respects to that observed following a single injection of a bacterial antigen.[4]

Another reticuloendothelial cell whose morphology and function are affected by adrenal cortical steroids is the lymphocyte. Lymphocyte dissolution and degeneration, with a resultant decrease or involution of lymphoid tissue, is known to occur following a wide variety of stresses. In many instances, this decrease in lymphoid tissue mass has been demonstrated to be based on the augmented rate of pituitary-adrenal cortical secretion caused by the stress. This is illustrated strikingly, for example, by the involution of lymphoid tissue which occurs in fasted animals but not in fasted animals which have been previously adrenalectomized.[5,6]

In the normal animal, shedding of lymphocyte cytoplasm and lymphocyte dissolution may be accelerated as a consequence of increased pituitary-adrenal cortical secretion,[3] and the constituents of this cell thus released to the lymph and eventually participate in metabolic transformations.[7,8] One of the constituents of lymphocytes has been demonstrated to be identical with the normal serum gamma globulin.[7,8,9] In the immunized animal, this fraction of the serum proteins frequently contains antibody, and it has now been demonstrated that the lymphocytes of the immunized animal contain antibody.[10,11] The release of protein from lymphocytes, and perhaps other cells, as a result of an increased concentration of circulating adrenal cortical steroids

may be an important aspect of the contribution which these hormones make to carbohydrate formation from protein.

It should be emphasized that hormones affect the rates of physiological reactions which may continue, albeit at a slower than normal rate, in the absence of the endocrine secretions. Removal of the thyroid gland does not result in a complete cessation of metabolism, but reduces it to a much lower rate or level. Also, experimental removal of the pituitary gland, which exerts a profound control over certain other endocrine organs, does not prevent life from continuing for almost normal periods of time, although again at a greatly reduced operating level. Conversely, the release in the organism of excessive amounts of certain endocrine products, or increasing their concentration by administration from without, results in acceleration of reactions normally influenced by those hormones. This is seen, for example, in data demonstrating that injection of adrenal cortical steroids, or increased secretion of these hormones as a result of pituitary adrenotrophin injection, produces an elevation of antibody titer either in a hyperimmunized animal or in a previously immunized animal with no circulating antibody.[8,12,13] These experiments suggest that the physiological basis of the anamnestic response is the pituitary-adrenal cortical control of lymphocyte structure and function. This would explain why various unrelated stimuli produce an anamnestic response. The maximum increase in antibody titer in the blood occurs at a time after hormone injection when the degree of lymphocyte dissolution is maximal. On the other hand, it has been observed recently that antibody production does not cease in the adrenalectomized animal.[14,15]

The results which have been obtained establish a partial basis for the role of the adrenal cortex in immunity, with particular reference to antibody formation. It may be pointed out that antibody production may be of two types: 1) that resulting from the reaction of the antigen with cells of the reticuloendothelial system, and 2) that arising as a result of the proliferation of antibody-containing cells, i.e., lymphocytes.[16] It is not unlikely that the equilibrium which obtains between these two types of antibody production in the normal organism may be altered in both the hormone treated and the adrenalectomized animal. Moreover, the data which have indicated a role for the adrenal cortex in antibody production have considered only one aspect of the problem, namely, antibody release from lymphocytes. It should be emphasized

that the concentration of antibody in the circulation at a particular time is probably a reflection of a state of dynamic balance among at least three metabolic processes involving antibodies: 1) synthesis, 2) release from antibody-containing cells, and 3) peripheral removal or utilization. It remains for future investigations to evaluate fully the contribution which each of these reactions makes to determining the level of circulating antibody under a variety of circumstances. Hormonal secretions could influence the rates of all of these processes, and removal of an endocrine gland may result in antibody production rates which are not necessarily the antithesis of those seen following injection of the hormone produced by that gland.

The demonstration that the lymphocyte is one of the end cells of adrenal cortical steroid action serves to integrate the role of the lymphocyte and the adrenal cortex in resistance. The control exerted by pituitary-adrenal cortical secretion over the contribution of the lymphocyte to immune globulin production is related to a specific type of resistance, immunity based on antibody formation. Whether this endocrine-lymphocyte relationship contributes to other types of resistance or immunity remains to be investigated. It is possible that the spontaneous involution of the adrenal cortex in man which begins during the second week of extra-uterine life may be the causative factor of the lowered immunity in infants during this age period. The value of adrenotrophin or adrenal cortical steroids, or of a physiological non-specific stimulus of the type of very small doses of epinephrine, as a method of increasing immunity in the human, is worthy of study and remains to be evaluated clinically.

In conclusion, a few comments may be made regarding the role of certain other endocrine glands in immunity. Clinical and experimental evidence has suggested that thyroid secretion is concerned with lymphoid tissue growth, and since this tissue is apparently an important site of antibody formation, the thyroid gland may contribute to at least a specific type of immunity. Evidence is now available that lymphoid tissue growth, after involution of these structures, is retarded in the absence of the thyroid.[6,15] Finally, the role of the sex hormones in immunity may now be interpreted, in part, in terms of the effects of these hormones on pituitary-adrenal cortical activity. Physiological doses of estrogens will generally augment, while larger amounts of estrogens produce inhibition, of pituitary adrenotrophin secretion. Androgen ad-

ministration will also generally diminish pituitary-adrenal cortical activity. It is not unlikely that sex differences in immunity, both natural and experimentally produced, may be related in part to the diverse actions of estrogens and androgens in influencing the level of pituitary-adrenal cortical secretion. The endocrine glands and their hormonal actions exhibit a high degree of integration and correlation in metabolism. As a consequence, the endocrine response to a particular stress may affect many diverse physiological processes which contribute to the immunity of the organism. Investigations of these processes in relation to endocrine secretions will make possible a more complete evaluation and understanding of the phenomena of natural resistance, of which immunity is one important aspect.

REFERENCES

1. Long, C. N. H. and Fry, E. G. Effect of epinephrine on adrenal cholesterol and ascorbic acid, *Proc. Soc. Exper. Biol. & Med.*, 1945, *59*:67.
2. Sayers, G., Sayers, M. A., Fry, E. G., White, A. and Long, C. N. H. Effect of adrenotrophic hormone of anterior pituitary on cholesterol content of adrenals, *Yale J. Biol. & Med.*, 1944, *16*:361.
3. Dougherty, T. F. and White, A. Functional alterations in lymphoid tissue induced by adrenal cortical secretion, *Am. J. Anat.*, 1945, *77*:81.
4. Conway, E. A. Reaction of lymphatic tissue of rabbits to Bacterium monocytogenes, *J. Infect. Dis.*, 1939, *64*:217.
5. Dougherty, T. F. and White, A. Role of the adrenal cortex in lymphoid tissue involution produced by inanition, *Anat. Rec.*, 1945, *91*:269.
6. White, A. and Dougherty, T. F. Role of the adrenal cortex and the thyroid in the mobilization of nitrogen from the tissues in fasting, *Endocrinology*, 1947, *41*:230.
7. White, A. and Dougherty, T. F. Pituitary adrenotrophic hormone control of rate of release of serum globulins from lymphoid tissue, *Endocrinology*, 1945, *36*:207.
8. White, A. and Dougherty, T. F. The role of lymphocytes in normal and immune globulin production, and the mode of release of globulin from lymphocytes. *Ann. New York Acad. Sc.*, 1946, *46*:859.
9. Kass, E. H. Occurrence of normal serum gamma-globulin in human lymphocytes, *Science*, 1945, *101*:337.
10. Dougherty, T. F., Chase, J. H. and White, A. Demonstration of antibodies in lymphocytes, *Proc. Soc. Exper. Biol. & Med.*, 1944, *57*:295.
11. Harris, T. N., Grimm, E., Mertens, E. and Ehrich, W. E. Role of lymphocytes in antibody formation, *J. Exper. Med.*, 1945, *81*:73.
12. Dougherty, T. F., Chase, J. H. and White, A. Pituitary-adrenal cortical control of antibody release from lymphocytes, *Proc. Soc. Exper. Biol. & Med.*, 1945, *58*:135.
13. Chase, J. H., White, A. and Dougherty, T. F. Enhancement of circulating antibody concentration by adrenal cortical hormones, *J. Immunol.*, 1946, *52*:101.
14. Eisen, H. N., Mayer, M. V., Moore, D. H., Tarr, R. and Stoerk, H. C. Failure of adrenal cortical activity to influence circulating antibodies and gamma globulin, *Proc. Soc. Exper. Biol. & Med.*, 1947, *65*:301.
15. *Unpublished results.*
16. Dougherty, T. F., White, A. and Chase, J. H. Relationship of antibody content of normal and malignant lymphocytes, *Proc. Soc. Exper. Biol. & Med.*, 1945, *59*:172.

CLINICAL AND EXPERIMENTAL STUDIES ON ADRENAL CORTICAL HYPERFUNCTION*

LOUIS J. SOFFER

Associate Attending Physician, Mount Sinai Hospital

THE adrenals in mammals and man consist of two glands united together. The two component parts, the medulla and the cortex, are developmentally and histologically entirely unrelated and are derived from two distinct and different parent tissues which unite only secondarily. The cortex is derived from the mesoderm and is closely associated with the urogenital mass, while the medullary tissue is derived from the ectoderm and has a common origin with the cells constituting the sympathetic nervous system. Although the cortex and medulla exercise entirely different functions, the recent studies of Long and his group indicate that the activity of the cortex is at least to some extent influenced by the functional integrity of the medulla. This relationship is evidenced by the fact that the medullary secretion, epinephrine, causes a release of adrenocorticotropic factor from the anterior lobe of the pituitary gland, which in turn stimulates the adrenal cortex.

The adrenal cortex is an organ of many functions. It plays a very vital role in salt and water and carbohydrate metabolism. It is intimately concerned with growth and muscular response. Evidence has been accumulating to indicate that it is important in the maintenance of normal blood pressure, and that it is probably very significant in the pathogenesis of certain types of hypertension. It has long been established that this organ is essential in resistance to stress and more recently that it is of prime importance in immunological responses. In addition it exercises a profound effect on the functions of other endocrine glands, notably the thyroid, gonads, and anterior lobe of the hypophysis. In short, the adrenal cortex plays a most active and important part in many vital bodily functions. Indeed, it is essential to life and its complete ablation, either experimentally or clinically, results

* Lecture delivered at the Graduate Fortnight, The New York Academy of Medicine, October 8, 1947.

in death unless substitutive therapy is administered.

The experimental removal of the adrenal glands in animals, or their total destruction through disease in man, results in a fairly well defined clinical picture which in effect represents the total disorganization of those functions which are normally dependent on the integrity of the cortex. Thus there occurs the usual loss in sodium with its attendant fluid loss, the characteristic disturbance in carbohydrate metabolism with either overt or subclinical hypoglycemia, the hypotension and asthenia, the increased susceptibility to infection, and the marked intolerance to stress. But in approaching the problem of adrenal cortical hyperfunction the situation is quite different and infinitely more complicated. This difference is in part due to the fact that there is no one hormone or mixture of hormones which actually represents complete replacement therapy. This lack renders it impossible at present to induce experimentally a state of adrenal cortical hyperactivity in its entirety. The most that one can accomplish with the hormones available is to note their individual effects when injected into normal or adrenalectomized animals. Although the information thus gained is important, it is by no means adequate since many of the signs and symptoms observed in patients with adrenal cortical hyperfunction cannot be experimentally duplicated. It is reasonable to expect, however, that with the further isolation of adrenal cortical fractions this problem will become progressively more clarified. Until such time we must utilize, in addition, the information obtained by the investigation of clinical material.

Here, too, however, the problem is complicated by the diversity of manifestations presented by patients with adrenal cortical hyperfunction. This lack of a consistently uniform clinical picture is probably due to the fact that the adrenal cortex consists of several different types of cells with varying functions. Thus, the studies of Greep and Deane and their co-workers strongly suggest that the zona glomerulosa is concerned with the elaboration of the salt and water hormone, while the work of Blackman, although much less conclusive but also provocative, points to the reticular zone as the origin of the sex hormones. It would appear, therefore, that the signs and symptoms presented by the patient are dependent on which cells are involved and stimulated by the hyperplastic or neoplastic process and which are destroyed by the same process with a consequent loss of their secretions.

The best clinical example of adrenal cortical hyperfunction is provided by the patient with an adrenal cortical tumor. This disease may then be used as a starting point from which to study the disturbance in physiology resulting from adrenal cortical overactivity. With this as a point of departure it promptly became apparent that a variety of pathological processes located in the adrenal or elsewhere were capable of producing a picture indistinguishable from that observed in patients with adrenal tumors. The point to be emphasized is that whether the basic disease process is an adrenal cortical tumor or hyperplasia, or a pituitary or thymic tumor, or hypothalmic disease, their respective clinical effects are mediated essentially through the adrenal cortex.

In a broad sense, the manifestations of cortical hyperfunction fall into two large categories consisting of 1) sexual, and 2) metabolic abnormalities. The sexual disturbances are characterized by pseudohermaphroditism, precocious sexual development, the development of hirsutism, changes in the voice, enlargement of the clitoris, decrease in the size of the breasts and amenorrhea in the females, while feminization and loss of libido are observed in adult males. The metabolic aberrations consist of the appearance of marked obesity which is generally curiously distributed, hypertension, plethora, disturbances in carbohydrate metabolism, osteoporosis, the appearance of purplish striae on the abdomen, flanks, breasts, arms or thighs, polycythemia, acne, and the development of a characteristic moon-like facies. The symptoms of the first group are generally referred to as the adrenogenital syndrome, while those of the second group are known as the Cushing syndrome. Patients with adrenal cortical disease may manifest predominantly the adrenogenital syndrome, the Cushing syndrome, or a combination of both. The sharp emphasis on the distinction between the two groups of symptoms is by no means entirely of academic interest. The distinction is of considerable practical significance, since the ultimate prognosis is considerably affected by these considerations. The life span of the patient who shows virilism alone is considerably longer and the outlook very much better than is the case with the patient who shows evidence of Cushing syndrome. In the latter group the contralateral adrenal is always atrophic either grossly or functionally, and the operative risk associated with the removal of the tumor is prohibitively high. On the other hand, in those patients with an adrenal cortical tumor whose major manifestation is virilism, the con-

tralateral adrenal is perfectly normal, and the removal of the tumor can be effected without any grave operative hazards. The operative mortality following the removal of the tumor in patients with Cushing syndrome is also influenced by the character of the tumor. The removal of a malignant tumor is much less hazardous than that of a benign one. The probable reason for this is that in the former group metastases occur early and by the time surgical removal is attempted viable metastases are already present.

The clinical picture which develops with adrenal cortical hyperfunction is in part dependent on the age and sex of the patient. When adrenal cortical hyperplasia or tumor occurs in utero in females, pseudohermaphroditism usually results. Pseudohermaphroditism is characterized by the presence of the gonads of only one sex, but associated with this are such abnormalities of the external genitalia as to render the identification of the sex through external examination doubtful. Frequently, pelvic inspection of the gonads has to be resorted to in order to establish the sex of the patient. Pseudohermaphroditism should not be confused with true hermaphroditism, since the latter is an embryological defect unrelated to any abnormalities of the adrenal cortex and characterized by the presence of the gonads of both sexes in the same person.

When the disease develops in children up to the age of puberty, the resulting clinical picture is quite different. Female children thus afflicted may manifest sexual precocity, the development of hirsutism of the face and limbs, enlargement of the external genitalia and breasts and deepening of the voice. Occasionally the only or major manifestation may be unusual obesity. In most instances there is a temporary period of rapid growth. This is, however, followed by an early closure of the epiphyses, and the patient generally remains short in stature. Menstruation as a rule does not occur even in older children who may have attained puberty, although several notable exceptions have been reported.

Male children with this illness generally show marked muscular and sexual development. They grow rapidly, develop signs of virilism with excessive hirsutism of the face, arms, and pubis. The size of the genitals may assume adult proportions. Genital maturation as a rule does not occur, although spermatogenesis has been observed. Occasionally, as with girls, obesity has been the outstanding manifestation of

the disease. The metabolic disturbances characteristic of Cushing syndrome are not infrequently observed in children along with the sexual abnormalities.

The clinical picture in women is usually characteristic and readily identified. They develop obesity which is generally limited to the face, upper part of the back, and the abdomen. The upper and lower extremities remain thin. The face assumes a rounded puffy plethoric appearance, described as "moon-like." There is an excessive growth of hair on the face, extremities, and abdomen. The breasts shrink in size, the clitoris may enlarge, amenorrhea develops, and the general muscular and skeletal configuration may approximate that of the male. The voice becomes deep, due to the elongation and thickening of the vocal cords. There is generally a loss of libido, but not infrequently their sexual interests are diverted to other females. In addition they may manifest hypertension, generalized osteoporosis, striae, polycythemia, and acne. The disturbance in carbohydrate metabolism is characterized by the presence of hyperglycemia, glycosuria, and a diabetic glucose tolerance curve. In short, these patients generally present a fully developed picture of both the adrenogenital and Cushing syndrome. Occasionally the predominant picture is that of virilism with little or none of the Cushing counterpart.

Adrenal cortical hyperfunction in adult males usually results in the production of Cushing's syndrome with some feminization, or they present signs of marked feminization with comparatively few manifestations of the metabolic abnormalities. Thus, they may show a thinning of the hair, the skin becomes delicate and soft, the genitals decrease in size, and there is a loss of libido. In many instances the breasts become quite large, and rarely a milky colustrum-like fluid is secreted. It is of interest, that while prepuberal boys, girls, and women all show signs of marked virilization, in adult males some degree of feminization is the rule.

These, then, in brief are the clinical syndromes produced by adrenal cortical hyperfunction. The fact that disease of the adrenals is capable of inducing such marked and unusual physical changes dealing with very fundamental processes attests to the primary role that they play in the body economy. With the biochemical techniques available to-day these syndromes present a unique opportunity to unravel the physiological role of these organs.

The adrenal cortex is the site of manufacture of three large groups of hormones: 1) Those dealing with electrolyte and water metabolism; 2) Those dealing with carbohydrate and protein metabolism; and 3) The sex hormones. There are many factors which influence the secretory activities of the adrenal cortex, but all of these factors operate through mediation of the anterior lobe of the hypophysis. In addition, the adrenal cortex is capable of autonomous function. It is true that following the experimental removal of the anterior hypophysis adrenal cortical activity is seriously impaired, but it is not entirely lost. This point is important if we are to explain the clinical picture resulting from an adrenal cortical tumor. The actual increase in size of the adrenal mass results in an increase in formation of the various cortical fractions, and hence the production of the characteristic syndrome. It is in effect immaterial as to whether the total increase in hormone is due to an actively secretory local tumor or due to increased secretory activity resulting from stimulation by the adrenocorticotropic factor of the anterior pituitary. The point which is important is that the clinical picture is determined by the amount of adrenal cortical hormone or hormones formed. It is on this basis that we can understand why the adrenogenital-Cushing syndrome may be produced by such superficially widely differing pathological processes as basophil tumors of the pituitary, malignant thymomas, tumors of the adrenals, and perhaps disease of the hypothalamus.

The sex hormones which have actually been isolated from the adrenal cortex of experimental animals are adrenosterone, 11-hydroxyisoandrosterone, 17-hydroxyprogesterone, and theelin. These compounds, with the exception of theelin, have androgenic activity, while the latter has a pronounced estrogenic effect. It does not necessarily follow, of course, that these hormones are identical with those elaborated by the human adrenal. This is a point difficult to prove, since it hardly lends itself readily to experimental study. The occasional attempt to isolate active sexual fractions from hyperplastic and tumorous adrenals has resulted in extremely meager yields. This may be due either to the fact that the present techniques are not adequate for the limited material available, or that only minute amounts of these substances are stored in the gland where they are manufactured. However, that the adrenals do manufacture such hormones is suggested by the marked decrease in the urinary excretion of various androgenic and estrogenic com-

pounds which follows the successful removal of an adrenal cortical tumor, or which occurs when the adrenals are destroyed by some pathological process, as in Addison's disease.

Under normal circumstances androsterone, dehydroisoandrosterone 3-α-hydroxyetiocholanone-17, pregnandiol, and estrogens are excreted in the urine. Of these, the first two have definite androgenic activity while the 3-α-hydroxyetiocholanone-17 is inert. These compounds have their origin in both the adrenal cortex and the male gonads. It has not been established that these are actually the compounds elaborated by the adrenal cortex. It is more likely that they represent degradation products of parent substances elaborated by the glands. In the presence of adrenal cortical hyperfunction not only is there usually an increase in the urinary excretion of these compounds but several additional ones have been isolated, including isoandrosterone, $\Delta_{3,5}$ androstadiene-17-one, 3-α-hydroxyandrosterone-17, and pregnane-3,17,20-triol. Of these compounds only the pregnane triols are probably inert.

The increase in the urinary excretion of both androgenic and estrogenic fractions which occurs in adrenal cortical hyperfunction is due to the excessive formation of these or parent substances. In the light of these observations one might expect that the degree of virilism or feminization displayed by the patient could be correlated with the urinary excretion of androgens and estrogens. But, surprisingly enough, such correlation does not always occur. Patients with virilism may excrete normal amounts of androgen, or even excessive quantities of estrogen. In some instances of adrenal cortical carcinoma with virilism, excessive quantities of androgen are excreted in the urine, and in at least one instance of marked feminization in a male due to a malignant adrenal tumor large amounts of estrogenic hormone were noted in the urine. However, even larger quantities of urinary estrogens have been observed in masculinized women. These observations are disconcerting, but it should be remembered that what we measure in the urine probably represents an overflow and is not necessarily an index of the amount of hormone actually utilized by the body. The thesis that virilism or feminization is due to excessive formation of the corresponding sex hormones is a reasonable one. The evidence, although admittedly confused and frequently contradictory, is at least suggestive.

The early observations dealing with adrenal cortical physiology demonstrated the significance of this organ in relation to electrolyte

metabolism, particularly the metabolism of sodium and water. With the experimental or clinical destruction of the adrenal cortex there occurred a loss of sodium from the intercellular tissue spaces, with a proportionate loss of fluid. There followed a loss in chlorides, an increase in serum potassium, and a reduction in CO_2 content. These electrolyte and fluid abnormalities were promptly corrected by the use of whole adrenal cortical extract and even more specifically so by the crystalline fraction—desoxycorticosterone. Further fractionation studies of adrenal cortical extract revealed that not all of the fractions isolated exercised a salt-retaining effect. Indeed, some compounds like 17-hydroxy-11-dehydrocorticosterone and 17-hydroxycorticosterone exercised a salt diuretic effect, while others, like corticosterone and dehydrocorticosterone, have only a minimal salt retaining effect. Desoxycorticosterone has no effect on carbohydrate metabolism, while those compounds like corticosterone, dehydrocorticosterone, and 17-hydroxycorticosterone which have either no effect on electrolyte metabolism or actually cause a salt diuresis, exert a marked effect on carbohydrate metabolism. The essential structural difference between compounds causing salt retention and those influencing carbohydrate metabolism is the presence of an oxygen atom at C_{11} in the latter instances. The presence of this oxygen, or hydroxyl group on C_{11}, while increasing the carbohydrate effect of the molecule, reduces its salt retaining effect. The salt diuretic fractions evidence a further structural difference in that they have an hydroxyl group on C_{17}.

In view of the fact that the adrenal cortex normally elaborates such hormones, one might expect evidence of increased secretion of these fractions in clinical instances of adrenal cortical hyperfunction. As a matter of fact Anderson and Haymaker have demonstrated that extracts of the blood and urine of such patients were capable of prolonging the lives of adrenalectomized rats beyond the survival period of untreated controls. The salt retaining effect of 1 cc. of blood was found to be equivalent to 4 to 6 grams of fresh adrenal tissue. It is, therefore, surprising that electrolyte abnormalities do not occur consistently. Actually, an increase in serum sodium occurs in approximately 15 to 20 per cent of the cases, while a reduction in serum potassium is demonstrable in 25 per cent. As to whether a disturbance in the electrolyte pattern occurs in clinical cortical hyperfunction is probably dependent on two factors: 1) Whether those adrenal cortical cells which are con-

cerned with the secretion of the electrolyte fractions are involved in the hyperfunctioning process, and 2) A compensatory mechanism is unquestionably set up, which in some way minimizes or inhibits the effect of these hormones when they are being secreted in excessive amounts. A clue as to the nature of this compensatory mechanism is provided by some experimental studies conducted in our laboratory. It was observed that in normal individuals and in patients with Addison's disease the intravenous injection of salt following the intramuscular injection of a single dose of desoxycorticosterone resulted in a retention of injected salt above that which occurs following the injection of salt alone. Similar experiments, repeated in patients with Cushing's syndrome on the other hand, resulted in a salt diuresis. Here, then, is the curious paradox of a hormone which under one set of circumstances causes a salt retention which is its expected and orthodox effect, while under other circumstances it produces a salt diuresis. It would seem then that in some instances of adrenal cortical hyperfunction the injected desoxycorticosterone either stimulates the secretion of a salt diuretic fraction or is itself converted into such a fraction. In view of the close chemical similarity between the salt retaining and the salt diuretic hormones, such a conversion appears quite feasible.

Clinically various electrolyte disturbances may be observed in hypercorticalism. There may occur an increase in blood sodium with or without an associated reduction in serum potassium and chlorides, or these latter changes may be present alone. A pathognomonic change, which is however only infrequently observed, consists of a reduction in serum chlorides and potassium, an increase in serum sodium with a marked alkalosis. The alkalosis, with the lowered chlorides and potassium may also occur with a normal serum sodium level. It is interesting to note that when a reduction in chlorides occurs this is always associated with a decrease in the blood potassium level. This is in contrast to the condition ordinarily observed in Addison's disease in which the chlorides vary with the sodium level and are entirely independent of fluctuations in the potassium values. In hypercorticalism the fluctuations of serum chlorides closely parallel those of the potassium. The administration of potassium either parenterally or orally will result not only in an increase in serum potassium but also that of chlorides, while the administration of chlorides will affect the serum levels of neither ion.

While serum electrolyte disturbances occur in somewhat less than

half the patients with adrenal cortical hyperfunction, alterations in carbohydrate metabolism occur more frequently, although by no means uniformly. The patients may develop frank hyperglycemia with glycosuria, or, much more commonly, the disturbance may be less overt and be manifested only by an abnormal glucose tolerance curve which assumes a diabetic pattern. The diabetes of adrenal cortical hyperfunction is difficult to control, since it is not as readily responsive to insulin and to the usual dietetic measures as in the case with true diabetes. On the other hand, severe diabetic ketosis has not been observed in this disease.

The disturbance in carbohydrate metabolism is probably dependent upon two factors. The first is the relation of the adrenal cortex to protein catabolism, and the second is the effect of the various adrenal cortical fractions on the peripheral oxidation and utilization of glucose. Since the adrenal cortex normally manufactures hormonal fractions which influence carbohydrate metabolism, it is a reasonable assumption that the disturbance in carbohydrate metabolism observed in hypercorticalism is due to excessive formation of these fractions. It is essentially immaterial whether the increased formation of these hormones is due to an increase in the number of the secretory cells such as occurs in adrenal tumors or whether it is due to increased secretory activity of the adrenal cortical cells secondary to the stimulating effect of adrenocorticotropic hormone of the adenohypophysis. The end result in both conditions is the same, in that larger amounts of cortical carbohydrate fractions are formed.

The adrenal cortex plays an important role in the breakdown of tissue protein and its conversion into glucose and glycogen. The brilliant work of Houssay and Biossoti, Long and his co-workers, Cori and Cori, Britton and Silvette, and Evans have clarified the nature of the mechanism involved. Fasting adrenalectomized rats excrete much less nitrogen than do normal rats under similar circumstances. The administration of cortical extract or its crystalline carbohydrate fractions results in not only an increase in liver glycogen and glucose but there is in addition a parallel and proportionate increase in urinary nitrogen. Since these changes occur under fasting conditions in both normal and adrenalectomized animals, it follows that both the increase in carbohydrate stores and the urinary nitrogen are due to the endogenous breakdown of protein. An even clearer demonstration of this phenomenon is provided by phlorhizin experiments. Phlorhizin lowers

the renal threshold for glucose so that sugar is excreted in the urine as long as there are available sources of sugar, be these sources endogenous or exogenous. Under normal circumstances glycosuria occurs even in the fasting animal. However, in the adrenalectomized phlorhizin treated animal glycosuria is markedly diminished. The administration of adrenal cortical extracts to such animals despite the continuation of the fast results in a marked increase in the glycosuria with a proportionate increase in urinary nitrogen.

The further effect of the adrenal cortex and its crystalline fractions on carbohydrate metabolism is provided by the studies on hypophysectomized and depancreatized dogs. The diabetes resulting from ablation of the pancreas is favorably modified either by the removal of the hypophysis or by bilateral adrenalectomy. The administration of anterior pituitary extract or adrenocorticotrophic factor causes a reappearance of glycosuria and hyperglycemia provided the adrenals are intact. In the absence of the adrenals, no such effect is evident. However, the administration of adrenal cortical extract to the depancreatized animal will induce glycosuria and hyperglycemia both in the hypophysectomized and in the adrenalectomized state. The glycosuria, here too, is associated with a parallel increase in the urinary excretion of nitrogen. In the light of these studies the conclusion is inescapable that at least part of the effect of the adrenal cortex on carbohydrate metabolism is related to its ability to break down proteins and help in their conversion to glycogen and glucose. That this phenomenon occurs in an exaggerated fashion in patients with adrenal cortical hyperfunction is evidenced not only by the disturbance in carbohydrate metabolism but also by the fact that these patients are in negative nitrogen balance indicating excessive tissue destruction.

The second important factor in the disturbance in carbohydrate metabolism in Cushing's syndrome is related to the peripheral utilization of glucose. Certain adrenal cortical fractions, notably 17-hydroxy-11-dehydrocorticosterone, inhibit the utilization of sugar by the peripheral tissues. The administration of this compound to adrenalectomized-depancreatized dogs results in an increase in glycosuria not accompanied by a proportionate increase in urinary nitrogen, indicating that part of the glycosuria is due to the inability of the tissues to utilize glucose satisfactorily.

In the light of these observations, the refractoriness of the diabetes

in Cushing's syndrome becomes understandable. There is a constant available source of endogenous glucose which is not capable of being entirely oxidized by the tissues. Dietary restrictions would appear futile in view of the fact that endogenous glucose is being formed excessively, while the effect of insulin is minimized by the peripheral action of the cortical hormones.

Osteoporosis, so commonly seen in Cushing's syndrome, is probably a reflection of the disturbance in carbohydrate metabolism. It was originally assumed that the osteoporosis was due primarily to the effect of the pituitary on the parathyroid bodies. It was thought, therefore, that the presence of decalcification was evidence of the absence of an adrenal cortical tumor and favored the diagnosis of primary pituitary disease. With the accumulation of more clinical material it became evident that osteoporosis occurred with equal frequency in both primary and secondary adrenal cortical hyperfunction. Histological and biochemical studies have failed to reveal any evidence of true parathyroid abnormalities. In the early stages of the disease hypercalcinuria is occasionally observed, but in general the calcium balance studies are quite normal. This is equally true of the blood calcium and phosphorus levels. The histology of the bony changes observed in Cushing's syndrome is quite different from that of those seen in hyperparathyroidism in that the former never manifest the cystic changes and giant cell tumors so characteristic of the latter. In addition, there is no evidence of any reparative process in the bones in Cushing's syndrome, while some new bone formation does take place in the osteoporotic areas produces by parathyroid rumors.

There are probably two factors responsible for the osteoporosis in hyperadrenal corticalism. As was originally pointed out by Albright, the excessive protein breakdown and conversion into carbohydrates causes a depletion in the formation of bone matrix which is essentially a protein substance. This lack of bone matrix limits the amount of calcium which can be deposited for the formation of new bone. In addition, there is a failure to absorb sufficient calcium and phosphorus from the intestinal tract to permit retention of these ions. Because of this, some calcium and phosphorus are actually withdrawn from the bony skeleton to make up for this lack. Thus, there is not only impairment in the ability to absorb the necessary basic ions for the manufacture of bone, but there is an inability to deposit these substances for their proper utilization.

The large majority of patients with Cushing's syndrome have osteoporosis, although the degree of decalcification may vary considerably. The osteoporosis may involve the skull, ribs, spine, and, less frequently, the long bones. The decalcification in these structures may be mild and roentgenologically questionable, or it may be severe enough to produce spontaneous fractures of the ribs and compression fractures of the vertebrae. In general, the osteoporosis observed in Cushing's syndrome is not particularly characteristic and is indistinguishable from that produced by other causes. The only exception to this are the changes described by Sussman and Copelman occurring at the anterior ends of the lower ribs just lateral to the costochondral junction. The rib in this region is expanded to about twice its normal diameter and is homogenously increased in density. This increase in density is reminiscent of that observed in callus formation, and actually cannot be distinguished from the latter roentgenologically, although no fracture line is demonstrable. These changes in the ribs are observed very infrequently, but when present are very suggestive of Cushing's syndrome.

Hypertension occurs almost uniformly in patients with hyperadrenalcorticalism. The causal mechanism of the hypertension is obscure, but we may speculate profitably concerning the role of certain of the adrenal steroids in this respect. Desoxycorticosterone, one of the adrenal cortical fractions, is capable of producing hypertension when given in relatively large amounts over a prolonged period of time. This effect is observed in the normal and in the bilaterally adrenalectomized animal, as well as in normal individuals and in patients with Addison's disease. It is of interest, however, that this hypertensive effect is elicited much more readily in the absence of adequate adrenal function than in normal individuals or animals. The fact that elevations in blood pressure following the use of desoxycorticosterone, occur more readily in the presence of destroyed or ablated adrenals suggests that some compensatory mechanism is operative under normal circumstances which inhibits to some degree the hypertensive effect of this hormone. The nature of this substance is at present unknown. Whole adrenal cortical extract, which is a combination of various adrenal cortical fractions, is, however, incapable of inducing hypertension. This would suggest that the inhibitory factor is in all probability an hormonal product of normal adrenal cortical activity. It may be postulated that the hypertension in Cushing's syndrome is due either to the excessive manufacture of a

hypertensive fraction or the reduction in formation of the inhibitory or balancing hormone. It is possible that the hypertensive factor is a desoxycorticosterone-like compound, since this is the one adrenal cortical steroid, isolated to date, capable of producing abnormal elevations in blood pressure.

The hypertension in Cushing's syndrome may reach alarming levels. When it has persisted for a considerable time, secondary eye ground, renal, and cardiac changes take place. In that event the associated phenomena are no different from those observed in the usual severe hypertensive cardiovascular disease. Narrowing and nicking of the retinal vessels, exudates and hemorrhages are frequently observed in the fundi. Renal and cardiac failure, as well as cerebral accidents, may occur. Experimentally, with desoxycorticosterone, Selye and Hall have succeeded in producing renal changes in fowl and mammals similar to those seen in nephrosclerosis.

The diagnosis of adrenal cortical hyperfunction is based on the history, the physical appearance of the patient, and on certain laboratory procedures. It should be emphasized that not all patients who have hirsutism or who are obese have overt adrenal cortical disease. If these manifestations indicate some degree of adrenal cortical overactivity, they represent physiological variants. In patients in whom the history and physical examination suggest the possibility of this disease, the following laboratory determinations are available to aid in establishing the diagnosis: 1) Determination of blood electrolytes, particularly Na, Cl, K, and CO_2; 2) The salt tolerance test; 3) Colorimetric determination of the neutral urinary 17-ketosteroids and 11-oxyketosteroids; 4) The biologic assay of the urinary glycocorticoids; and 5) The demonstration of an adrenal mass by intravenous pyelography or by peri-renal insufflation.

Some abnormality in the blood electrolytes will occur in half the instances of adrenal cortical hyperfunction. The absence of such abnormalties does not mitigate against the diagnosis. A considerable increase in serum sodium or depression in serum potassium bespeaks adrenal cortical hyperfunction but does not help in localizing the pathology or in differentiating between tumor and hyperplasia. The salt tolerance test is significant only when positive—that is when the injection of desoxycorticosterone and salt under controlled conditions results in a sodium and chloride diuresis—and in that instance the result is

pathognomonic of adrenal cortical hyperfunction. As is the case with the blood electrolytes, the salt tolerance test is of no value in determining the nature or locus of the underlying pathology.

The term "17-ketosteroid" applies to those steroids with a ketone group on the 17th carbon atom. These neutral 17-ketosteroids form the urinary products of androgenic metabolism and arise from substances produced by the adrenal glands and the male gonads. They are further divided into alpha and beta fractions, which refer to the spatial position of the 3-hydroxyl group. The beta ketosteroids are readily precipitated by digitonin and are thus separated from the alpha members. The latter substances are elaborated by both the adrenal cortex and the male gonads, while the beta fractions are manufactured entirely by the adrenal cortex. In normal individuals only 10 to 15 per cent of the total urinary ketosteroids consists of the beta fraction. In normal urines the alpha ketosteroids include androsterone and 3-α-hydroxyaetiocholanone-17, while the beta ketosteroids include dehydroisoandrosterone and isoandrosterone.

The daily urinary excretion of total neutral 17-ketosteroids varies with the age and sex of the patient. The values are somewhat higher for adult males than for females, and are considerably higher in general after adolescence. In adrenal cortical hyperfunction the urinary excretion of the 17-ketosteroids may be normal or increased. In general, excessive quantities are excreted in the presence of an adrenal cortical carcinoma, while in benign adrenal cortical tumors the urinary values may be normal. The large amounts excreted in cortical carcinoma are due essentially to an increase in the beta fractions. In adrenal cortical hyperplasia there is frequently a moderate increase in the urinary 17-ketosteroids. In summary, therefore, a normal urinary excretion of the 17-ketosteroids is not evidence against the diagnosis of adrenal cortical hyperfunction, since such values may be obtained in benign adrenal cortical tumors and in virilism or Cushing's syndrome without any overt adrenal cortical pathology. A marked increase in the urinary excretion of these compounds almost always indicates adrenal cortical carcinoma, while a moderate increase is observed in both carcinoma and hyperplasia.

The 11-oxy-ketosteroids are those compounds with an oxygen grouping on the 11th carbon atom. In a general way they parallel the urinary excretion of the 17-ketosteroids, but there are instances of adrenal cortical hyperfunction in which the urinary excretion of the

11-oxy compounds is increased while the values for the 17-ketosteroids remain within the normal limits.

The term "urinary glycocorticoids" refers to those compounds manufactured by the adrenal cortex which exercise an effect on carbohydrate metabolism. They parallel the urinary excretion of the 11-oxy-ketosteroids. They are generally excreted in large quantities in the urine of those patients who excrete excessive amounts of the neutral 17-ketosteroids. But here also there are not infrequent instances in which there is no parallel between the urinary excretion of the glycocorticoids and the 17-ketosteroids.

In adrenal cortical hyperfunction excessive quantities of estrogens or androgens may be excreted in the urine, as determined by biologic assay.

In the interpretation of the results of the urinary excretion of these compounds it must be borne in mind that the results are significant only if the compounds are excreted in abnormal amounts. Normal urinary values may not be used as an argument against the diagnosis of hyperadrenalcorticalism, although they rather point against the diagnosis of adrenal cortical carcinoma. The urinary presence of large quantities of these substances strongly favors the latter diagnosis, while a moderate increase would suggest hyperplasia but may also occur in carcinoma or even in the case of benign tumors.

Since the prognosis and treatment are so largely dependent on the underlying pathology, it is important to determine whether the patient has an adrenal cortical tumor or hyperplasia or primarily pituitary disease. Rarely, an abdominal tumor may be palpated. Not infrequently an adrenal mass can be identified by intravenous pyelography. Generally more definitive aid can be obtained by peri-renal insufflation. This method consists of the roentgenologic study of the abdomen after peri-renal insufflation with oxygen. By this technique the adrenals are well outlined and the presence of a tumor or enlargement is more readily demonstrable. Wilhelm recently suggested the use of laminography in peri-renal insufflation and found the combined technique superior to films made after simple peri-renal insufflation in delineating the normal adrenal gland and its lesser enlargements.

The treatment of adrenal cortical hyperfunction is determined in greater part by the nature of the underlying pathology. In general the therapeutic measures consist of the use of various hormonological agents

such as testosterone or estrogens, the use of x-ray treatment to the pituitary and adrenals, and finally surgical intervention.

Albright was the first to demonstrate the beneficent effects of large doses of testosterone. Following its use the patients became stronger, they developed a positive nitrogen balance, the osteoporosis and the hirsutism were lessened, and in general the patients were reported to show considerable improvement. Unfortunately, our experience has not been so satisfactory. All our patients were treated with testosterone before being subjected to more hazardous procedures. In no instance could we demonstrate any definite change, other than perhaps some decrease in the asthenia. Our results with estrogens have been equally discouraging.

Irradiation of the pituitary in instances of pituitary basophilism with or without associated adrenal cortical hyperplasia has its proponents. There are unquestionably well documented, although isolated, instances in which the results have been dramatic and curative. By far and large, however, this therapeutic measure has generally been unsuccessful. Again, all the patients in our series were subjected to pituitary irradiation before surgery was resorted to, without any success. However, because of the occasional good response and the great hazards attendant upon surgery, both testosterone and pituitary irradiation should be tried first. The results with x-ray treatment of the adrenals have been uniformly unsuccessful.

The surgical approach directed to the adrenals is a complicated and hazardous one, but if successfully executed results in cure. The greatest danger lies in the removal of a benign adrenal cortical tumor producing Cushing's syndrome. In these instances the contralateral adrenal is atrophic and the removal of the tumor results in a curious shock-like state in which the mortality rate is inordinately high. This shock is not that of the usual Addisonian crisis, in that it ensues directly after operation despite the pre- and postoperative administration of large amounts of adrenal cortical extracts and parenteral fluids. In addition, the blood electrolytes are normal in spite of the critical condition of the patient. Nor does the shock represent a hypoglycemic episode, since the blood sugar levels are generally well within the normal range. This postoperative state unquestionably represents the sudden deprivation of some adrenalcortical fraction or fractions as yet unidentified, which are vital to the body economy. In the presence of virilism alone—that is where

there are none of the metabolic disturbances characteristic of Cushing's syndrome—the removal of a benign adrenal cortical tumor is a fairly safe procedure. The difference in operative risk between this group and that with Cushing's syndrome is due to the fact that in the former the opposite adrenal is perfectly normal, and hence the removal of the tumor does not actually deprive the organism of any vital fractions.

When the adrenal cortical tumor is malignant its removal is somewhat less risky than when it is benign. This is particularly true when the tumorous growth has penetrated the capsule. These patients tend to survive the operative procedure in part because the tumor is not actually completely eradicable locally, and in part because distant metastatic spreads have already occurred in most instances. The local and distant metastases represent viable cortical tumor tissue which prevents the development of acute adrenal insufficiency. Unfortunately these patients eventually succumb to the malignant process, although they may show a dramatic regression of the symptoms for a short while after the removal of the primary tumor.

There is a great deal of difference of opinion concerning the advisability of operating on patients with adrenal cortical hyperfunction in whom the underlying pathology is that of bilateral adrenal cortical hyperplasia. The surgical procedures advocated in this group involve the removal of one hyperplastic gland, or the removal of one whole gland and half of the other, or the removal of half of each gland. The procedure employed in our clinic has been the removal of one of the hyperplastic adrenals, and our experience has been quite satisfactory, although the numbers are too small from which to draw any definite conclusions. The operation is not particularly hazardous although technically rather difficult since most of the patients are obese and the surgical approach difficult. The postoperative course is stormy during the first twenty-four to forty-eight hours, but we have had no fatalities to date. The therapeutic response has been good, with a considerable regression of the signs and symptoms.

The preoperative preparation and the postoperative care of the patients is of extreme importance. This applies particularly to those patients with benign adrenal cortical tumors, but is only slightly less important in patients with malignant cortical tumors or cortical hyperplasia. The preoperative preparation consists of the use of liberal quantities of whole adrenal cortical extract and the lipoid fraction now

commercially available and the administration of parenteral isotonic saline in 5 per cent glucose. These measures are instituted on the morning of the operation and continued throughout the operation and postoperative period until the patient is well out of danger. One must be on the alert for the development of certain therapeutic complications, especially peripheral and pulmonary edema. These complications are more likely to ensue following the excessive use of desoxycorticosterone than with whole adrenal cortical extract. In either event, if peripheral or pulmonary edema develops both the extract and the parenteral fluids must be discontinued temporarily.

COLITIS*

Z. T. BERCOVITZ

Assistant Clinical Professor of Medicine, New York Post-Graduate Medical School (Columbia University), Instructor in Medicine, Cornell Medical School, New York, N. Y.

COLITIS has been used loosely to cover all conditions of dysfunction of the bowel. This is erroneous. The term "colitis" specifically refers to inflammatory lesions of the colon. It does not include the various forms of bowel dysfunction in which there is no inflammation.. It should be pointed out that while dysfunction often is manifested in inflammation of the bowel, not all dysfunction is associated with or caused by inflammation. It is suggested that the term "colitis" be reserved for only those lesions of the colon in which there is inflammation.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of inflammatory lesions of the bowel involves a clear-cut understanding of the difference between bowel dysfunction, which is not associated with any pathological changes, and lesions of the colon, which are either specific or non-specific in character.

It has been shown by Bercovitz,[1,2,3] in a series of studies on cellular exudates of bowel discharges, that the mucus or bowel evacuations from a healthy colon contain no significant cells. On the other hand, the presence of cells of various types, especially polymorphonuclear leukocytes, round cells and macrophages, is indicative of pathological changes, even though these may not be visualized through the sigmoidoscope or in roentgen-ray films made with contrast media.

The best way to obtain specimens for examination is to give three saline enemas to cleanse the bowel of fecal matter. The mucus or other material evacuated about one hour after the last enema is then examined. The mucus should be examined immediately after passage first on the warm stage for evidence of motile amebae, and then by means of Loeffler's methylene blue wet preparations for the study of cellular

* Read before the Friday Afternoon Lecture Series, New York Academy of Medicine, December 6th, 1946.

elements. The patient with simple bowel dysfunction has no cellular exudate.

Inflammatory lesions of the bowel which enter into the differential diagnosis of "colitis" may be classified as follows:

I SPECIFIC
- *Bacterial* (Shigella group (bacillary dysentery), cholera, and other organisms whose role is not clearly understood, such as various streptococci and Escherichia coli)
- *Protozoan* (Endamoeba histolytica, Endolimax nana, Balantidium coli, Girardia lamblia and Plasmodium falciparum)
- *Helminthic* (Schistosoma mansoni, S. japonicum)
- *Virus Infections* (Lymphopathia venereum)

II NON-SPECIFIC
- *Chronic Ulcerative Colitis* (cause unknown)
- *Diverticulitis*
- *Ileitis* (regional, terminal ileo-colitis)
- *Nutritional Deficiencies*

III OTHER CONDITIONS TO BE RULED OUT
- *Psychosomatic*
- *Malignancy of the Gastrointestinal Tract*
- Gastric, gall bladder or pancreatic disease, and diseases of the genito-urinary tract

General Management of Colitis

The management of inflammatory disease of the bowel includes not only specific therapy, when indicated, but also treatment of the patient as a whole. The success of any program of therapy will depend upon the extent to which each of these is carried out.

In the general management of the colitis patient, psychosomatic factors and the nutritional state of the patient should be evaluated.

Since it is often impossible to state with certainty to what extent the psychogenic factors are responsible for the colitis and resulting bowel dysfunction, it is of the greatest importance that the patient and his problems be carefully evaluated and every effort made to establish a definite anatomical diagnosis. It is unfair to both the physician and the patient to make the diagnosis of psychoneurosis without prolonged painstaking investigations in order to establish the correct diagnosis. Consultations with other physicians, who have not seen the patient

previously and are therefore not too strongly aware of the psychoneurotic factors, are helpful.

The colitis patient cannot be treated casually or in a hurry. It may require weeks or months of observation before the true nature of the disease manifests itself. The physician must take time to understand his patient and win his confidence. It is only by carefully observing his patient, listening sympathetically to his story and encouraging him to release his worries and cares, that the physician can win his patient's confidence to be rewarded ultimately by being able to make a diagnosis. Often there are social aspects, intimate family and marital problems, financial difficulties, and even small worrysome matters, which are related to the problem, and it is a great comfort and benefit to the patient to know that the attending physician is concerned, understands and is anxious to help.

The physician should under no condition tell the patient that he is psychoneurotic, but rather should reassure him that his complaints are quite normal. It should be remembered that any patient who has diarrhea, pain in the abdomen, with loss of weight and strength over a period of time, is bound to become neurotic and distressed over points which would ordinarily be insignificant. Furthermore, the physician should be aware that the psychoneurotic manifestations of bowel disease are frequently the first indication that there is anything wrong with the patient.

Every patient with bowel dysfunction should be given proper treatment, even though the symptoms appear to be purely psychosomatic in origin. This is imperative, since the various types of bowel dysfunction are frequently the precursors of bowel diseases. Therefore, if the physician bears in mind that his patient with bowel dysfunction is a candidate for actual gastrointestinal pathology, including inflammatory changes and malignant degeneration, many of the late effects may be eliminated.

The general nutritional condition of the patient is the second important factor to be considered in the management of colitis. This includes careful evaluation of fluid balance, proteins, carbohydrates and vitamins. These apply not only to the acute dysenteries and diarrheas, but also to chronic conditions, especially chronic ulcerative colitis.

The therapeutic indications are for a minimum of 2500 cc. of fluids in 24 hours. This should be given by intravenous infusion for the first

day or two in cases of acute diarrhea. The use of 5 per cent glucose in normal saline is most acceptable, and in most instances 500 cc. of plasma should be given at least once during the day. To each infusion of 1000 cc. may be added 100 mg. thiamine chloride, 100 mg. niacinamide and 1000 mg. ascorbic acid. This program of fluid administration should be carried on simultaneously with specific therapeutic agents.

Whole blood transfusions are of great value both in patients with acute and chronic diarrhea, and in patients with inflammatory disease of the bowel, such as acute or chronic bacillary or amebic dysentery and chronic ulcerative colitis.

Dietary in the acute and chronic inflammatory diseases of the bowel has been a subject of great controversy in the past few years. For a long time it was the consensus that every consideration should be toward maintaining a non-irritating diet and to provide food which does not have any residue or roughage in order to put the bowel at rest and thus reduce the number of bowel movements in the day.

The patient with an inflammatory disease of the colon has bowel movements of blood, mucus and pus because of the inflammation, especially of the rectum and sigmoid, and not simply because of the food he may eat. Food taken into the stomach will provoke a defecation reflex as a purely physiological reaction. This is shown in cases in which ileostomy or colostomy has been performed. It is not the irritation caused by any single food, but the inflammation of the bowel which causes the diarrhea. This mechanism of the defecation reflex should be carefully explained to the patient so that he will not fear eating and will cease attributing every desire to evacuate the bowels to the foods taken into the stomach.

The dietry indications in acute and chronic inflammatory diseases of the bowel are for a full, balanced diet, particularly rich in proteins and vitamins. The foods should be prepared and served attractively, with every effort made to approach the normal diet. The practice of serving all foods in pureed form is unfortunate. Giving the patient food he can chew helps both psychologically and physiologically. More than ten years of experience in following this practice has proved it is without harm to the patient. Moreover, patients state that they feel better and have less abdominal distress when maintained on a liberal diet.

The only contraindications in diet are highly spiced foods and members of the cabbage and onion families. Food should be prepared simply,

well cooked and flavored to the patient's taste. It is best to give frequent small feedings, each containing an adequate amount of highly nutritious food.

Hydrochloric acid has been found of great value as a digestive aid. A dose of 30 minims in one-half of a glass of water after each meal is indicated. Other drugs, except as specifically indicated in the various infections, are generally contraindicated. Opiates give slight, but very temporary relief, and have the disadvantage of being habit-forming. Most patients state that while the opiates give some relief in the number of evacuations, there is distention, abdominal distress, and ultimately profuse movements which leave the patient weaker than if the drug were not given. Sedation with small dosages of barbiturates is indicated in highly nervous patients, and such preparations as syntronal, belladonal and bellergal seem to give relief and comfort at times.

Vitamin preparations are of value, and the selection should be based on potency and palatability. Parenteral injection is indicated wherever there is a question about absorption from the gastrointestinal tract. This is the method of choice during the acute stages.

Specific therapy, wherever indicated, will be considered under the various types of bowel inflammation.

Bacillary Dysentery (Colitis)

Bacillary dysentery (colitis) is an acute inflammatory disease of the large bowel caused by one of the Shigella group of organisms. The intensity of the infection and the clinical picture varies within wide limits, depending partly upon the virulence of the infecting organism and upon the resistance of the patient at the time of the infection.

The usual clinical picture is outstanding and characterized by the sudden onset of diarrhea with straining, tenesmus, blood, mucus and pus. The patient is toxic, feverish, and has bowel movements numbering 20, 30 or more a day. The patient is literally glued to the bedpan, and after great effort expels only a small amount of mucus and pus which stick to the bedpan.

On sigmoidoscopic examination, the bowel is found to be inflamed, necrotic, with definitely ragged ulcerations usually in the transverse axis of the bowel. Heavy, purulent, mucoid material is present, which on microscopic examination shows a heavy cellular exudate of polymorphonuclear leukocytes, denuded epithelial cells and macrophage cells

—all with ringed nuclei and with many toxic granules. It is possible to make a presumptive differential diagnosis between amebic and bacillary dysentery on the basis of cellular exudate studies. Cultural examinations made early in the disease directly from the ulceration will usually yield organisms of the Shigella group.

The therapeutic indications in bacillary dysentery (colitis) are twofold: namely, specific to eradicate the causative Shigella organism, and general systemic to improve the general condition and comfort of the patient.

Specific therapy involves the use of one of the sulfonamide drugs. Sulfaguanidine has been shown to have a specific therapeutic action in bacillary dysentery; but sulfadiazine, used in various parts of the world where sulfaguanidine was not available, was found to have an equally specific action. In fact, in the author's experience in India, sulfadiazine became the drug of choice, and the response noted was as dramatic as that obtained with sulfaguanidine and equally as specific.

The recommended dosage of sulfaguanidine in the treatment of acute bacillary dysentery is 3 or 4 grams initially, followed by 2 grams every three hours day and night for the first 24 hours or until the bowel movements become less frequent, the straining and tenesmus are relieved, and there is a passage of fecal material. After the first 24 hours, the midnight dose may be omitted. It has been found that by the end of the second day the patient will have made sufficient progress to warrant reduction of the dose to 1 gram every four hours. This dosage should be continued for at least four or five days even though the patient appears to be symptom free.

Most noteworthy in the author's wartime experience with bacillary dysentery was the fact that patients made dramatic recoveries, as evident from symptomatological improvement and sigmoidoscopic findings, but did not have the tendency to develop chronic ulcerative colitis, as previously seen so frequently after bacillary dysentery infection. It was found that after a week of sulfaguanidine or sulfadiazine, proctoscopic examination revealed an entirely normal bowel mucosa with negative cellular exudate on study of the bowel discharges.

The general systemic approach to the treatment of bacillary dysentery is equally as important as the specific chemotherapy. The patient should be given by intravenous infusions 5 per cent glucose in normal saline. To each 1000 cc. may be added 100 mg. thiamine chloride, 100

mg. niacinamide and 1000 mg. ascorbic acid. A minimum of 2000 cc. should be given intravenously until the patient is able to take adequate fluids by mouth. In addition, 500 cc. of plasma should be given intravenously during the first 24 hours, making a total of 2500 cc. of fluid injected the first day of treatment. Sedatives of the phenobarbital group may be administered, but the opiates, including paregoric, tincture of opium, are not only unnecessary but contraindicated. In most instances the patients appear more toxic and have more abdominal distress after the opiates. The response to sulfaguanidine or sulfadiazine is so prompt and effective that the opiates are unnecessary.

The diet should be high in proteins and vitamins, and the patient should be encouraged to eat solid foods and take fluids by mouth at the earliest possible moment. This is most important, since the patient with profuse diarrhea, is losing proteins and vitamins which must be replaced. If it is remembered that the bowel movements are caused by the inflammation of the sigmoid and colon, and not by the food the patient eats, many patients will be saved from starvation, which often results because proteins and vitamins are not replenished as they are lost.

Amebic Dysentery (Colitis)

Amebic colitis is caused by an infection with Endamoeba histolytica. In its simplest form, there is typical ulceration with a normal mucosa surrounding. The amebic colitis may be either acute or chronic. In the acute stages the symptom picture is quite characteristic, with diarrhea amounting to 4, 6 or 8 bowel movements in 24 hours and with no straining nor tenesmus. The patient is only moderately ill, and is not as toxic as in bacillary dysentery; generally there is no fever. The bowel movements are usually copious and may or may not contain visible mucus and blood.

In those cases in which the infection has persisted for a considerable length of time and has become chronic, the clinical picture varies within very wide limits, and it is quite impossible to describe a so-called typical or classic picture of chronic amebiasis. There may be alternating diarrhea and constipation, some flatulence with more or less gas, and vague abdominal pains are frequently present which makes the patient conscious of his abdomen. Constipation is not an infrequent symptom of amebiasis; in fact, there are a great many patients who claim that they have never had an attack of diarrhea but have suffered only from con-

stipation.

The diagnosis depends upon finding the typical forms of E. histolytica in specimens of the stool or other bowel discharges. In making the diagnosis, the various concentration tests should be used, especially the Faust centrifugal flotation with zinc sulphate or Otto's modification of the technique. If these methods fail to reveal amebae, then the patient should be given saline enemas, and freshly passed mucus examined for amebae. The patient also may be given a dosage of Epsom salts, and the stools passed in the laboratory so that they can be examined fresh and warm.

In evaluating the mucus specimens, it should be remembered that there are many cells which come down in the bowel discharges and which may be confused with E. histolytica. These are most frequently macrophages, polymorphonuclear leukocytes, epithelial cells and plasma cells, and cause confusion especially in freshly passed, unstained material. Cells of tissue origin should be carefully identified to avoid mistaking them for E. histolytica. Ofttimes chronic ulcerative colitis, carcinoma of the colon, especially the rectum or sigmoid, and lymphogranuloma are treated as chronic amebiasis and the real nature of the condition missed until it is too late to help. To avoid such instances of mistaken diagnosis, the findings should be confirmed by those qualified in the differential diagnosis, especially by fixed stained preparations.

It should be pointed out that there are cases of chronic amebiasis of long duration in which it may not be possible to demonstrate forms of E. histolytica in the stools. This is particularly true of some of the complications of amebiasis, such as amebic granuloma, amebic hepatitis and amebic typhilitis. In these instances the diagnosis must be made on the basis of clinical history, physical findings and the response to specific therapy with emetine.

Sigmoidoscopic examination may show only a moderate degree of atrophy of the bowel mucosa; occasionally, there may be typical amebic ulcerations; or there may even be a normal rectum and sigmoid with the lesions being present higher up in the bowel. There may be secondary bacterial infection of the bowel such as in bacillary dysentery, in which case the sigmoidoscopic picture is that of the acute process.

The complications of amebiasis have been outlined by Bercovitz[4] and include secondary bacterial infection of the amebic ulcerations, perforation of the bowel, amebic hepatitis with or without abscess for-

mation, amebic granulomata especially of the sigmoid or cecum, amebic appendicitis, typhilitis, and the more uncommon complications of amebic abscess of the spleen following perforation of the splenic flexure of the colon, and amebic abscess of the brain and lungs. Amebic abscess of the prostate has been seen.

The therapeutic approach to the problem of amebic colitis and its complications must include a careful evaluation of the patient as a whole and treatment of the patient, and not only his parasites. It should be remembered that in more than 90 per cent of the cases of acute amebiasis studied there is some secondary bacterial infection of the bowel, and in about 50 per cent there is evidence of amebic hepatitis. Thus every patient should be carefully studied for evidences of secondary infection, such as cellular exudates in the bowel discharges in amebiasis, liver tenderness, thickening of the bowel over the cecum or descending colon and sigmoid area.

Table I is taken from a recent article by Bercovitz[4] and summarizes the drugs most commonly used in therapy of amebiasis.

Emetine is the most valuable drug in amebiasis, and is indicated in both the acute and chronic stages of infection, as well as in complications. Where the infection is of long duration the parasites tend to get deep into the tissues, and in such cases emetine in addition to oral medication is indicated. In cases of failure, it is not a question of the parasites being "emetine-fast," but rather a problem of secondary bacterial infection which makes it impossible for the drug to reach the parasites. The same applies to other drugs used in the treatment of amebiasis.

On the basis of the author's experience, the following course of therapy has been found most acceptable and results in complete eradication of the infection. A course of emetine is given simultaneously with a course of sulfadiazine for seven days. This is then followed by a course of 200 tablets of diodoquin. The sulfadiazine may then be repeated once and followed again by the diodoquin. Diodoquin is the drug of choice in that it causes the least amount of irritation with highest efficiency. The most important point to remember is that the dosage must be adequate. Therefore, a dosage of 200 tablets given in doses of 4 tablets four times daily (16 tablets for the total daily dosage) is used. Under this program there have been no failures.

TABLE I—TREATMENT OF AMEBIC DYSENTERY‡

Drug	*Single Dose*	*Number of Doses Daily*	*Total Daily Dosage*	*Total Dosage of Single Course of Treatment*	*Indications*
Emetine hydrochloride*	½ gr. (0.032 Gm.) Subcutaneously	2 (a.m. and p.m.)	1 gr. (0.0065 Gm.)	7 gr. (0.455 Gm.)	Acute and chronic amebiasis, amebic granuloma, hepatitis, typhilitis perforations
Diodoquin Tablets of 3.2 gr.	4 tablets	4 (four times a day after food and bedtime)	16 tablets (3.84 Gm.)	200 tablets (64.00 Gm.)	Acute and chronic amebiasis with trophozoites and cysts of E. histolytica
Chiniofon Tablets of 0.25 Gm. each.	2-3 tablets	3 (three times a day after food)	6-9 tablets (1.5-2.25 Gm.)	100 tablets (2.50 Gm.)	Chronic amebiasis, cyst passers
Vioform Tablets of 0.25 Gm. each.	3 tablets	3 (three times a day after food)	9 tablets (2.25 Gm.)	100 tablets (25.0 Gm.)	Acute and chronic amebiasis with cysts of E. histolytica
Carbarsone† Capsules of 0.25 Gm. each	1 capsule	2 (a.m. and p.m.)	2 capsules (0.5 Gm.)	20 capsules (5.0 Gm.)	Chronic amebiasis, with cysts

* Myocardial poison—give subcutaneously only. Never to be given by intravenous or intramuscular injection. Blood pressure and pulse should be checked before each injection. Patient should be kept at bed rest if possible.

† Carbarsone is an arsenical and should not be used in any cases suspected of liver damage, such as amebic hepatitis.

‡ Reproduced by permission of the New York State Journal of Medicine.

Chronic Ulcerative Colitis

Etiology: The etiology of chronic ulcerative colitis is still obscure, despite the large number of studies made. An extensive analytical review of the literature on the etiology of chronic ulcerative colitis published by Ginsberg and Ivy,[5] revealed that there is no single etiological factor responsible for all cases.

Chronic ulcerative colitis as a disease entity may follow many disease conditions. Amebic and bacillary dysentery have been followed by this disease; indeed, there are certain cases in which these infections might seem to be the precipitating agents. Undoubtedly emotional and psychogenic factors are concerned, but it is difficult to attribute sole cause to them. There have been many instances in which great emotional and psychological upsets have been attended by attacks of diarrhea with dysfunction of the bowel, and in such instances when the condition persists over a long period of time, it is conceivable that permanent bowel damage may occur.

Although the causative agent in chronic ulcerative colitis has not been established, it is essential to conduct prolonged and intensive investigation of all the possible factors and to give the patient the benefit of the various specific therapeutic measures available.

Complete investigation of cases of chronic ulcerative colitis involves repeated careful microscopic examination of exudates both before and after saline enemas for amebae, cellular exudate studies with Loeffler's methylene blue, sigmoidoscopy to rule out malignancy, cultures of mucus and bowel discharges for pathogenic microbes, and finally, roentgen-ray examination of the colon with the barium colon enema. In addition to these, it is essential to make gastric analyses and to determine plasma ascorbic acid, prothrombin clotting time, plasma proteins and glucose tolerance. These studies will in many instances give the therapeutic indications for the patient as a whole.

Treatment: Treatment of chronic ulcerative colitis consists of two parts, much in the same way as that of treating other forms of colitis: (1) treatment of the patient as a whole, and (2) treatment directed against the specific infection of the bowel.

As previously stated, psychological and emotional factors must be considered in the management of chronic ulcerative colitis as they are in other forms of colitis. The patient who has chronic diarrhea, ab-

dominal pains, anorexia, nausea, and the general debility which goes with the disease, is also affected psychologically and becomes emotionally unstable.

Patients with chronic ulcerative colitis must be understood to be helped. It is imperative that under no circumstances are they made to feel that they are mental cases. They should be encouraged and repeatedly told that they will be cured and be normal again. Every sign of encouragement should be stressed, even if it is temporary, and the physician should never display his discouragement. The family physician must employ practical psychotherapy. The patient should be given time to talk and ask questions, each of which should be answered whenever possible.

In addition to creating mental rest and peace of mind in his chronic ulcerative colitis patient, the physician should employ physical rest and relaxation. Narcotics and habit-forming drugs should be avoided. Opium has been a favorite drug to reduce bowel movements, but it is ineffective except as a temporary measure and has the disadvantage of becoming habit-forming. Many a patient with chronic ulcerative colitis has become an addict because of the unfortunate use of forms of opium. This practice should be eliminated. The barbiturates are much more satisfactory, but they, too, may be habit-forming. No matter what drug is used for sedation, it is important not to continue it for too long a period.

Nutrition and Diet: Maintenance of proper nutrition of the patient is the major problem confronting the physician treating a case of chronic ulcerative colitis. It must not be forgotten that the patient has a diarrhea and moves his bowels with blood, mucus and pus because he has an inflammation of the bowel, especially of the recto-sigmoid area, and that he does not move his bowels because of the food taken into his mouth and swallowed which may evoke a defecation reflex.

The physician should be prepared to dispel the erroneous belief of many patients that because they have diarrhea following any single meal it is to be attributed to the food consumed. This is important to ward off the ill effects of elimination of essential foods from the diet, when there is no just cause other than the patient feels it is the food he eats that causes the diarrhea.

The practice of giving perfectly bland diets to remove all roughage from the colon has not cured the inflammatory lesions of chronic ulcera-

tive colitis. In fact, it has been noted that even when an ileostomy has been performed and the colon put entirely at rest in so far as fecal matter is concerned, the patient still passes blood, mucus and pus from the rectum because of the inflammation present.

There is ample evidence to show that patients with chronic ulcerative colitis are soon depleted of their reserves of proteins, vitamins and other essentials for nutrition and tissue repair. The therapeutic indications, therefore, are for an adequate, liberal diet with enough proteins, carbohydrates and vitamins to replenish the losses suffered from the disease and the diarrhea. It should be remembered also that the patient with chronic ulcerative colitis does not absorb adequate amounts of food even though it is not possible to demonstrate roentgenologically any lesions of the small bowel. Thus the nutritive content of his diet must be increased to replace his losses and to make up for the poor absorption of whatever food he does take in. It has been proved by experience that patients who take an adequate amount of food, not only feel better and are stronger, but they do not have as much abdominal distress.

The diet in chronic ulcerative colitis cases should include adequate amounts of proteins, especially meats. These should be dictated by the taste and desires of the patient. Beef steaks, roasts, chopped meats, boiled or broiled, and tastily served are excellent sources of essential proteins, and should form the basis of any chronic ulcerative colitis diet. Vegetables and fruits in keeping with the patient's likes and dislikes should also be served.

All food should be properly prepared and special attention should be given to serve the menu attractively, to stimulate the patient's appetite and desire for food. It has been a common experience that a patient will tolerate and eat many vegetables which are cooked and served in natural form, but will become nauseated at the sight of puréed spinach with butter, or other puréed and strained vegetables. Puréed vegetables may be disguised by using them in creamed soups, in which form they may be enjoyed; but it should be mentioned that the concept of serving puréed vegetables to prevent roughage and thus reduce bowel movements is without scientific foundation. On the contrary, experience has shown that the patient who eats an adequate amount of meats and vegetables does better and has less pain. The same applies to simple salads such as lettuce and well-ripened tomatoes, or fruit juices such as orange and grapefruit juice. The use of a whole orange or whole

grapefruit is to be encouraged, and in many instances it has been found that the serving of grapefruit revived the appetite of the patient and stimulated his normal eating pattern.

The rule, then, in the nutritional management of chronic ulcerative colitis is the administration of high protein, high carbohydrate, high vitamin diets with intermediate feedings as often as possible, and every effort made to avoid starvation with further depletion of the body tissues.

Intravenous Fluids: Parenteral administration of body fluids, proteins and vitamins is of indisputable value, and every patient should be given the benefit of such treatment. Intravenous infusions of 500 cc. of plasma once or even twice daily are indicated in severe cases. To each infusion may be added 100 mg. thiamine chloride, 100 mg. niacinamide and 1000 mg. ascorbic acid. Blood transfusions in amounts of 250 to 500 cc. at frequent intervals are invaluable. In severe cases the use of blood and plasma daily or every other day may be absolutely necessary to save life. It has been found that even chronic cases who are not moribund, but seem to be holding their own and maintaining a stationary course in their disease, may be helped considerably by parenteral administrations.

Intravenous infusions of glucose in normal saline are also indicated to maintain fluid balance in the patient. Vitamins in the same concentrations as in plasma infusions may be added to the glucose infusion. The total amount of fluid intake in cases of chronic ulcerative colitis should be a minimum of 2000 cc. daily.

The administration of parenteral injections should be determined by the physician after careful evaluation of the patient with respect to the number of bowel movements, the quantity of material passed, the nature of the evacuations, the diet and the amount of food consumed by the patient. Ofttimes despite the fact that laboratory reports indicate seemingly adequate numbers of erythrocytes or plasma proteins, there may be need for supplementary parenteral administrations when these factors are considered.

Specific Chemotherapy: The use of specific drugs in chronic ulcerative colitis has been disappointing up until the present time. This was adequately brought out in the symposium on the use of the sulfonamides in gastrointestinal diseases held by the American Gastroenterological Association and reported recently.[6] Neither the sulfonamides, nor

penicillin, nor streptomycin has been effective in bringing about cures. This has been the experience of all those who have followed their cases for sufficient time to make careful evaluation of their results.

The sulfonamides have been used extensively. It is true that in many instances there have been what seemed to be dramatic effects following the administration of the various forms of sulfonamides, but follow-up of these patients revealed no permanent "cures." However, the temporary beneficial effects noted would warrant the continued use of the sulfonamides provided the patient is carefully observed for untoward effects of these drugs and their use is not prolonged. It should be noted that merely changing the bacterial flora of the bowel contents is not sufficient to cure a case of chronic ulcerative colitis. The causal relationship of any single microörganism to chronic ulcerative colitis has not been demonstrated adequately as yet.

Penicillin and streptomycin have given disappointing results. Some patients receiving streptomycin seem to become worse. In my experience penicillin has not given even the temporary beneficial effects sometimes seen following the administration of the sulfonamides.

Evaluation of any Form of Therapy in Chronic Ulcerative Colitis: The evaluation of any form of therapy in chronic ulcerative colitis must be made with caution. Only after a large number of patients have been studied and followed over a period of not less than five years can any statement be made regarding the value of a particular form of therapy. The need for the use of placebo therapy prior to the actual medication is of the utmost importance.

Certain criteria for evaluation of therapeutic results are necessary and the minimum standards must be rigidly followed. The criteria for cure in this disease are divided into two main groups; namely the clinical symptomatology and the objective findings of the laboratory and sigmoidoscopic examination.

Clinical evaluation of response to therapy is always concerned with the psychological response of the patient to any new medication or new system of therapy. The patient's statement concerning the number of bowel movements, the character of the stools, should be carefully weighed and studied, until they are formed, normal in size and shape, and without blood, mucus, or pus present.

The matter of sphincter control is of the greatest importance, and also the number of night evacuations. Abdominal cramps, pains and

gas should disappear. Improvement in the general well-being of the patient, as well as in his appetite and weight are other factors to be considered.

Laboratory studies should reveal a reduction in the sedimentation rate and clearing of the cellular exudates of the bowel discharges. A normal sedimentation rate and bowel discharges without cells are the fundamental objective basis for a statement of cure or improvement in any case.

Sigmoidoscopy is of value but the personal enthusiasm of the examining physician must be considered. However, if there is loss of ulcerations, clearing of the submucous hemorrhagic areas which are usually pin-point or larger in size, reduction in the edema, inflammation and thickening of the bowel mucosa, and the bowel becomes non-friable and will not bleed at the slightest contact with the sigmoidoscope when it is passed, then there is justification for an estimation of a cure. It should be pointed out that restoration of tone to the mucosa so that it is not friable is one of the last things to occur, and with it there is simultaneously a drop in the sedimentation rate and clinical improvement in the patient.

These standards represent the irreducible minimum for therapeutic evaluation in chronic ulcerative colitis. Not only must the patient be brought to this point to consider him cured, but he must remain in this condition for a minimum of five years. Otherwise it is impossible to state with certainty that the treatment was not given just at the time of a spontaneous remission, for such remissions have been observed up to five years.

Surgery in Chronic Ulcerative Colitis: The surgical indications in chronic ulcerative colitis have been stated clearly by Cave[7] and others. The more frequent use of ileostomy has been avoided because until the present time, it has been impossible to point to any considerable series of cases, in which it has been possible to reestablish the continuity of the bowel and return the patient to a normal bowel status. In most instances permanent ileostomy with its associated inconvenience has been a stumbling block. Patients therefore have been carried on a medical regime in the vain hope of reaching a period of remission which will be prolonged and that a form of "cure" will be effected.

Such practice has in most instances resulted in the patient's becoming so weak and so depleted that when finally ileostomy was considered,

the patient was in such poor condition that the surgical mortality of the operation is far out of proportion to what it should be from a purely technical standpoint. Furthermore, by the time ileostomy is considered, permanent damage to the bowel has taken place, and the pathological changes occurring may be irreversible so that the ileostomy becomes permanent with no chance for recovery of normal bowel function.

It is too early at this time, and the number of cases is too small, to predict what the end results will be of experiments now in progress in which active therapy has been undertaken of the distal loop of the bowel following ileostomy. The results observed at this time are a marked improvement in the well-being of the patient, a decline in the sedimentation rate, and improvement in the objective appearance of the bowel wall. Further reports on progress will be forthcoming.

It may be that for the benefit of the patient, ileostomy will have to be performed earlier so that active therapy can be instituted and it may be possible to reestablish continuity of the bowel in the future after healing is complete. If, however, the delay is too long and the pathological changes have become irreversible, then no means of therapy will cause healing.

Prognosis and Complications: The prognosis of chronic ulcerative colitis should always be guarded because of the complications which generally occur. These have been outlined by Ricketts and Palmer.[8] Under no circumstances is the true prognosis to be communicated to the patient or his immediate family. At all times the physician should hold out hope for eventual cure, and never display even the slightest doubt of the future lest the patient lose hope, quit fighting and die. There are thousands of cases of chronic ulcerative colitis who have become useful citizens and are performing useful functions in society even though they do not represent "cures."

The attending physician should be alert to such complications as perforations of the bowel wall. These may be minute, and as a rule are pin-point in character. They may result from the passage of infectious agents through the lymphatics to lodge in the bowel wall and cause a local area of peritoneal irritation with symptoms which point to a mild, more or less localized peritonitis.

The therapeutic indications in these cases is absolute rest in bed, the administration of one of the sulfonamides, preferably sulfadiazine, fluids by vein, and in cases where it is comforting, an ice bag.

In some instances the perforations may become larger, and actual abscesses may form along the bowel wall. These may become localized and well walled off, and under these conditions, it is better to treat the patient conservatively. If the bowel wall is so fragile that it has perforated spontaneously, the handling involved in finding the abscess and other manipulations may cause the death of the patient. Under these circumstances, there is no single surgical procedure which will cure the case, and as a rule other perforations are likely to occur. If an abscess becomes definitely localized and seems to be near to the abdominal wall, simple drainage may be considered, but even this is of great danger to the patient.

Stricture of the bowel is another complication which commonly follows a prolonged case of chronic ulcerative colitis. This may be single in the rectum or there may be multiple strictures in various parts of the bowel. When it is known that a patient has developed one or more strictures of the bowel, great caution must be observed to maintain the feces in a liquid state. If the patient is allowed to have a solid fecal mass, obstruction of the bowel will develop, which is most difficult to relieve.

It is possible to maintain a patient in good nutritional state for a period of years with two or three mushy bowel movements daily. This may be accomplished by means of carefully regulated dosages of milk of magnesia or sodium sulfate. Castor oil is contraindicated because of its constipating effect. One patient was thus maintained for eight years.

When roentgen-ray examinations of patients suspected of having bowel strictures are made, the roentgenologist should be informed so that he can use proper mixtures of barium and institute measures for elimination of the barium after the examination in order to avoid intestinal obstruction.

Carcinoma of the large bowel following chronic ulcerative colitis does occur, and has been variously reported by Cave,[9] and Ricketts and Palmer[8] and others. It would be expected that following a prolonged irritative lesion of the bowel, the incidence of cancer would be higher. On the other hand, hyperplastic changes of the bowel mucosa with polyp and pseudopolypoid changes are frequently observed in varying degree. In many instances, the entire bowel wall is involved in these changes, the process extending from the rectum to the cecum.

When this occurs, it is impossible to look forward to cure of the patient by ordinary medical measures. Such changes do not seem to progress into cancerous degenerations any more frequently than others. In a review of the available literature by Page and Bercovitz[10] it was found that among a total of 1,467 cases of chronic ulcerative colitis reported with statistics on its association with carcinoma of the colon, only 28 developed carcinoma of the colon—an average incidence of 1.9 per cent. In this connection, Swinton and Warren (referred to by Page and Bercovitz[10]) stated that they have never observed progression of the polypoid changes associated with ulcerative colitis to a malignant stage.

Helminthic Colitis and Lymphogranuloma Venereum

Helminthic colitis and lymphogranuloma venereum are dealt with briefly because they are relatively rare.

Infections with helminths, such as the various forms of Schistosoma, may be diagnosed first by consideration of the geographical location from which the patient has come, and then by careful studies of the stool for evidence of the organisms causing the infection. The specific diagnostic methods are discussed in textbooks of tropical medicine and parasitology, and more recently in publications coming from the U. S. Army Commission on Schistosomiasis. Treatment of infections with one of the forms of Schistosoma is by means of the antimony compounds, preferably fuadin.

Lymphogranuloma venereum is a specific virus infection which invades the lower bowel. It is more common in the female, but occurs also in males, especially after irregular sexual practices such as sodomy. In such cases there is usually a history of diarrhea, but on careful questioning it is revealed that the patient passes blood, mucus and pus from the rectum without any reference to the bowel movements; in fact, the patient who has had the disease for any length of time may actually be constipated as a result of the stricture which usually complicates the picture. The diagnosis is usually confirmed by proctoscopic examination, first by digital examination with notation of the stricture of the rectum within reach of the examining finger and the widely gaping anus from which there is a copious discharge of sanguinous pus and mucus. The mucosa is granular with innumerable tiny nodules, giving the finger the feel as though it were passed into a "bag of beans." The Frei test is positive.

Therapy of lymphogranuloma venereum of the rectum includes administration of the sulfonamides, especially sulfathiazole. If the stricture causes obstruction to the bowel, colostomy may have to be performed.

REFERENCES

1. Bercovitz, Z. Studies on cellular exudates of bowel discharges; control observations on 1123 patients, 7 autopsies and 3 dog experiments, *J. Lab. & Clin. Med.*, 1940, *25*:788.
2. Bercovitz, Z. Studies on cellular exudates of bowel discharges; the differential diagnosis of amebiasis. Types of cells found in bowel discharges of patients with bowel complaints, *Am. J. Digest. Dis.*, 1940, *7*:93.
3. Bercovitz, Z. Studies on cellular exudates of bowel discharges; the diagnostic significance of cellular exudate studies in chronic bowel disorders, *Ann. Int. Med.*, 1941, *14*:1323.
   Bercovitz, Z. Recent advances in the treatment of chronic ulcerative colitis, *M. Clin. North America*, 1940, *24*:683.
4. Bercovitz, Z. T. Complications of amebiasis. *New York State J. Med.*, 1946, *46*:2291.
5. Ginsberg, R. S. and Ivy, A. C.: The etiology of ulcerative colitis; analytical review of the literature, *Gastroenterology*, 1946, *7*:67.
6. Application of sulfonamides to gastrointestinol disease: Panel discussion by various authors, *Gastroenterology*, 1945, *4*:1.
7. Cave, H. W. Late results in the treatment of ulcerative colitis. *Ann. Surg.*, 1946, *124*:716.
   Cave, H. W. Surgical experiences with ulcerative colitis, *S. Clin. North America*, 1945, *25*:301.
8. Ricketts, W. E. and Palmer, W. L. Complications of chronic non-specific ulcerative colitis, *Gastroenterology*, 1946, *7*:55.
9. Cave, H. W. Cancer of the colon. *Bull. New York Acad. Med.*, 1944, *20*:255.
10. Page, R. C. and Bercovitz, Z. T. Chronic ulcerative colitis with terminal carcinoma of the transverse colon. Case report. *Submitted for publication.*